BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 6 1951

WILLIAM HARVEY AND THE SCHOLASTIC TRADITION*

BY

JAMES YOUNG, D.S.O., M.D., F.R.C.S., F.R.C.O.G.

Emeritus Professor in Obstetrics and Gynaecology, University of London

So many learned men have delivered orations on William Harvey that there is clearly little fresh in fact or opinion which can be said. I was to some extent encouraged to accept the task of delivering the oration this year, so generously conferred on me, because I knew that I could not be expected to propound any new views on Harvey's life, character, or achievements. My function would rather be the less ambitious one of suggesting a theme which would provide the occasion for our paying tribute once again to our great progenitor.

The compulsion imposed on a Harveian orator of living over a considerable period in close touch with the mind of his subject brings with it some pleasing and rewarding experiences. Among these I have personally most enjoyed the opportunity of living, as it were vicariously, through one of the momentous periods in the history of knowledge—that period, namely, when the human spirit had begun, at first painfully and then more confidently, to shake off the fetters of scholastic rule. Harvey is a grand exemplar as well as a grand companion with whom to re-live these fateful days, for he reveals for us in his writings so clearly the thoughts and beliefs, and withal the confusing intellectual loyalties, that then swayed the minds of men.

To understand Harvey's outlook and achievements we must remind ourselves that he was surrounded by those fertilizing influences on human thought which had their great flowering in the aesthetic and literary renaissance, first in Italy and then in Northern Europe, and which, during his own early life, had culminated in our Shakespeare. The same influences were abroad in science and philosophy, and it is no coincidence that Descartes, the founder of modern philosophy, Galileo, one of the great architects of modern science, and Harvey, the founder of experimental medicine, were contemporaries.

The Spirit of the Schools

At the same time we are constantly reminded by a study of the works of these great innovators that the spirit of the schools was still heavy upon them. We remember that Harvey was a student at Padua from 1598† to 1602, and that from that stronghold of Aristotelianism he carried back to England much of the outlook of Aristotle. Indeed, his biggest work, that on generation, is largely a treatise in the manner of the great philosopher. The text is based upon a similar text written by Aristotle 1,900 years before, the conclusions are largely a confirmation or modification of Aristotle's views, and the whole work is inspired by the veneration in which Harvey clearly held his master. In one place he exclaims: "Foremost amongst all the ancients I follow Aristotle; among the moderns, Fabricius of Aquapendente; the former as my leader, the latter as my informant by the way."‡ Fabricius, also a good Aristotelian, was Harvey's teacher at Padua. At another place he says: "The ancient philosophers . . . by their unwearied labour and variety of experiments, searching into the nature of things, have left us no doubtful light to guide us in our studies. In this way it is that almost everything we yet possess of credit to philosophy has been transmitted to us through the industry of ancient Greece."

It is of interest to place beside these remarks of Harvey the opinion of those who ascribe the intellectual thraldom of the Dark Ages to the teaching of the Greek philosophers. Bertrand Russell, in a reference to a statement of Aristotle, says: "This, like everything else that Aristotle said on scientific subjects, proved an obstacle to progress" (*History of Western Philosophy*, p. 551, Allen and Unwin, London, 1947). A great historian (H. A. L. Fisher), in a reference to the seventeenth century, says: "The centre of intellectual interest had changed. The prophetic genius of Francis Bacon was inviting the student to abandon Aristotle and the Scholastics and to turn to the obedient study of nature. Not by *a priori* reason but by induction were the secrets of the world to be unlocked" (*A History of Europe*, p. 641, Edward Arnold, London, 1938).

Francis Bacon has a special interest for the student of Harvey, as, according to Aubrey, Bacon and Harvey were known to one another, probably intimately, in their mutual relationship as patient and medical attendant. According to Aubrey, Harvey, "speaking in derision," said that Bacon "wrote philosophy like a Lord Chancellor." Whether this innuendo reflects the fundamental conflict in their respective philosophies we cannot say.

*The oration delivered at the 156th Harveian Festival in Edinburgh on June 1, 1951.

†D'Arcy Power in his *Life of Harvey* gives 1598 as the date when Harvey went to Padua. Herbert Spencer in his Harveian Oration (London, 1921) states that Harvey's name first appeared on the roll of Padua University in 1600, and he quotes Venn as stating in his *Annals of Caius and Gonville College* that Harvey was a scholar in that college till Lady Day, 1600.

‡This and subsequent quotations are from the *Works of William Harvey, M.D.*, translated from the Latin by Robert Willis and printed for the Sydenham Society, London, 1847.

Aubrey is not always reliable. Moreover, Harvey, in his twenty-fifth exercise, uses words which suggest that he did not despise the Baconian method. These come after his discussion on the development of the chick. This, he says, may have appeared too lengthy "to those who do not see the end and object of such painstaking, of such careful observation. Wherefore I think it advisable here to state what fruits may follow our industry, and in the words of the learned Lord Verulam, to 'enter upon our second vintage.'" On the other hand, Bacon does not mention Harvey in his published works. It is true that Bacon died (in 1626) before the appearance of Harvey's book on the circulation (1628), but it is difficult to believe that he had not learnt something of the important discovery during the many years in which Harvey was lecturing on it in London prior to its actual publication.

Attitude to Aristotle

In Bacon's own works we have clear evidence that in his attitude to Aristotle the difference between the two men was profound. In the *Novum Organum* Bacon says: "In the physics of Aristotle you hear hardly anything but the words of logic. . . . Nor let any weight be given to the fact, that in his book on animals and his problems, and other of his treatises, there is frequent dealing with experiments. For he had come to his conclusion before; he did not consult experience, as he should have done, in order to the framing of his decisions and axioms; but having first determined the question according to his will, he then resorts to experience, and bending her into conformity with his placets leads her about like a captive in a procession; so that even on this count he is more guilty than his modern followers, the schoolmen, who have abandoned experience altogether" (*The Philosophical Works of Francis Bacon*, p. 271. George Routledge, London, 1905).

We know that Harvey's whole outlook was in direct opposition to this view on Aristotle. Almost every page of his works, especially of the *De Generatione*, is to us a vindication of the philosopher. It would seem to be equally clear that Harvey was unconscious of any need to protect the good name of the Stagirite, and this encourages us in the belief that if he had knowledge of Bacon's hostility he did not regard it as worthy of active refutation. For we know that Harvey was not averse from active controversy where his convictions were assailed. At the same time he was sufficiently of his age to realize that the battle against blind subservience to authority had already been engaged. "When," he says, "we acquiesce in the discovery of the ancients, and believe . . . that nothing farther remains to be known, we suffer the edge of our ingenuity to be taken off, and the lamp which they delivered to us to be extinguished." And elsewhere he exclaims: "The method of investigating truth commonly pursued at this time therefore is to be held as erroneous and almost foolish. . . . We have frequently mere verisimilitudes handed down to us instead of positive truths." To Harvey the fault is not with Aristotle but with those for whom all knowledge was contained in the books of the sages written many centuries before or in the speculative inventions to which these books had given birth. As Ernest Barker remarks: "The Middle Ages inherited the Peripatetic Cult of the 'master'; they 'made his torch,' as Dryden said, 'their universal light'; and thus the beginning of modern science in the sixteenth century took the form of a revolt against Aristotle—one of the most scientific spirits that ever lived. The life of Aristotle after his death has many of the elements of tragedy" (*Encyclopaedia Britannica*, 14th ed., p. 353, London, 1929).

In his passionate advocacy of the direct approach to Nature and his wholesale condemnation of those who trafficked in "mere verisimilitudes" Harvey showed at once his hostility to the schoolmen and his plea for a return to the method of Aristotle. In this he had powerful company in René Descartes, the most outstanding of his early converts. In his *Discours de la Méthode* Descartes says of the pseudo-followers of Aristotle: "I am sure that those who most passionately follow Aristotle nowadays would think themselves happy if they had as much knowledge of nature as he had, even if this were on the condition that they should never attain to any more. They are like the ivy that never tries to mount above the trees which give it support, and which often descends again after it has reached their summit" (*The Philosophical Works of Descartes*, Vol. 1, p. 125, Cambridge University Press, 1911).

Work on Generation

It was by one of the great chances in the history of science that Harvey went to Padua in 1598 and there found Fabricius, a great anatomist, who was interested in the problems of the heart and blood vessels. After he left Padua in 1602 and during the following years, by patient and direct study in man and animals, apart from a lingering residue in the shape of the vital and animal spirits and the innate heat, which he took over from his predecessors, Harvey established the major facts in regard to the circulation. His book was not published till 1628. His largest work, with which I propose to deal more especially to-day, is the *De Generatione Animalium*. This was not published till 1651, when he was 73 years old. To this work Harvey devoted a great part of his life, for he already refers to it in his *De Motu*, published twenty-three years before. It is clear that he expended on it his great talents and his great energy. It contains a vast accumulation of observations, more particularly on the development of the chick. But in addition it refers to studies carried out on the generation of other animals, and it has been estimated that altogether over eighty different species were investigated. In the book Harvey refers to an extensive work on the generation of insects to which he attached great importance but which was lost when his house was attacked and his belongings were destroyed during the Civil War.

To the work on generation Harvey applied the same method of "controlled experiment" as he had employed in his study of the circulation. In the latter work the method was triumphant. The *De Motu* introduced a new era in the history of science. On the other hand, whilst in the study of generation many interesting facts and some facts of lasting importance were revealed, in general the permanent value of this work has been small. The chief reason is that for the study of the essential data Harvey was without the technical assistance necessary, more especially the microscope.

Harvey's Outlook

We know Harvey as a great innovator. But to appreciate him in the round we have to note the conservatism that was deep in his nature. At a time when many enlightened men were embracing the new cosmology, Harvey's outlook was firmly Ptolemaic. This cannot but be strange to us, since Galileo was teaching at Padua

when Harvey was a student there. It is true that Harvey left Padua in 1602 and Galileo's first publication in support of Copernicus was in 1613. But thereafter his views spread rapidly throughout Europe. Nevertheless, in the *De Generatione*, published in 1651, Harvey remarks: "As the sun, now in the East and then in the West, completes the measure of time by his ceaseless revolutions."

Harvey's cosmic background was essentially mediaeval. For him man and his earth were the centre and pivot of the universe round which the sun and stars revolved, bringing to man his day for work and his night for sleep, the seasons and all the influences that flowed in from the macrocosm on man, its epitome or microcosm. "For indeed," he says in one place, "all things seem to derive their origin from a celestial influence, and to follow the movements of the sun and stars"; or again: "The cock and the hen are especially fertile in the spring; as if the sun, or heaven, or nature, or the soul of the world, or the omnipotent God—for all these things signify the same thing—were a cause in generation superior and more divine than they; and thus it is that the sun and man, that is the sun through man as the instrument, engender man."

The cosmic order for Harvey was still undisturbed by the heresy of Galileo. It was the cosmic order of the astrologer mellowed by time and robbed of its sorcery and magic. For already there was coming into it an awesome sense of law. But it still retained its mediaeval pattern. We can, from the many allusions in his works, recognize that to Harvey nature, in all its varied operations, inanimate and animate, was the grand instrument of the supernatural powers, with its many functions delegated to a vast descending hierarchy of agencies, whose importance decreased in gradual diminuendo the farther their remove from the Prime Cause. It was the cosmic order which Shakespeare had enshrined in his memorable lines:

> The heavens themselves, the planets, and this centre
> Observe degree, priority, and place,
> Insisture, course, proportion, season, form,
> Office and custom, in all line of order:
> And therefore is the glorious planet Sol
> In noble eminence enthron'd and spher'd
> Amidst the other . . .
> . . . but when the planets,
> In evil mixture to disorder wander,
> What plagues, and what portents! what mutiny!
> What raging of the sea! Shaking of Earth!
> . . . . . .
> Take but degree away, untune that string,
> And, hark, what discord follows!
>
> (*Troilus and Cressida*, Act 1, Scene 3.)

These agencies had, as their handmaidens in the sublunary sphere for the performance of the different functions of the living organism, the three souls of Aristotle: the vegetative soul by which growth and reproduction are performed; the sensitive soul by which the organism appreciates and reacts, chiefly by motion, to its environment; and, in the case of man alone, the rational soul. Entering intimately into all life processes, as the corporeal means by which the incorporeal souls carry out their functions, there are the three spirits of Galen: natural, vital, and animal. It is possible that Harvey had departed from the grand triad of Galenical spirits, for in one place he says: "Physicians admit as many spirits as there are principal parts or operations of the body—viz., animal, vital, natural, visual, auditory, coneoctive, generative, implanted, influent, etc., etc." Amongst the greatest celestial gifts is that of the "innate heat," the *calidum innatum*, the gift of life itself.

His Handicap in Study

We have seen that Harvey was from the outset gravely handicapped in his study of the phenomena of generation by the lack of the microscope. As a result some of the most fundamental claims in the *De Generatione* are based upon error. Take, for example, his failure, after repeated and scrupulous study of the genital canal of the hen, deer, etc., to find any trace of seminal fluid after mating. He insists that "after intercourse there is nothing more to be found in the uterus, than there was before the act. And when this shall have been afterwards clearly established and demonstrated to be true of all kinds of animals, which conceive in a uterus, it will at the same time be equally evident that what has hitherto been handed down to us from all antiquity on the generation of animals, is erroneous; that the foetus is not constituted of the semen either of the male or female, nor of the mixture of the two, nor of the menstrual blood." This led him to what now seems to us as the monstrous error that fertilization takes place by a sort of immaterial contagion, a kind of spiritual influence "analogous to the essence of the stars," by "virtue of a divine agent as things are set fire to and blasted by a spark . . . or lightning." But to appreciate properly the workings of Harvey's mind we have to recognize clearly that this conclusion followed many careful and painstaking observations. It was a deduction that had the sanction of a truly scientific method. It was for Harvey a very important deduction, for it contradicted the Aristotelian view that the ovum arose from the fusion of the menstrual and seminal fluids. Moreover, it was in keeping with Harvey's continual preoccupation with the relative insignificance of the material elements in generation.

His Interpretation of "Matter"

His attitude to "matter" is to the modern reader one of the most interesting features of Harvey's outlook. For him the material cause in the processes of life comes low down among the four causes of Aristotle. I find it difficult to define exactly the Harveian interpretation of matter, although I have been to some pains in my attempt to understand it. Perhaps the viewpoint can be brought before the mind more vividly by a quotation from his discussion of the material source of the different parts of the body and on whether these are "both engendered and nourished by diverse matters (as other workers have maintained), either the blood or the seminal fluid; viz., the soft parts, such as the flesh, by the thinner matter, the harder and more earthy parts, such as the bones, etc., by the firmer and thicker matter."

Harvey will have none of this subservience to matter, this "prevalent error," as he calls it. "Nor do they err less," he says, "who, with Democritus, compose all things of atoms; or with Empedocles, of elements. As if generation were nothing more than a separation or aggregation or disposition of things." He has to accept the elements of Empedocles—air, earth, water, and fire—but these "so-called elements . . . are not prior to those things that are engendered, or that originate, but are posterior rather—they are relics or remainders rather than principles." It is "an argument of no great cogency to say that natural bodies are primarily produced or

composed of those things, into which they are ultimately resolved; for upon this principle some things would come out composed of glass, ashes, and smoke." For him the substance of life has a mystical unity, unsullied by any material contacts. It is "a mere homogeneous . . . jelly . . . and from this, under the law of generation . . . as by a divine fiat, from an inorganic an organic mass results." For Harvey the substance from which life takes its origin and its eventual shape is in its beginnings entirely homogeneous. To conceive it as containing within itself elemental differences as the basis for the subsequent development of the various organs is to endow the substance with a significance which it does not possess and to abrogate the power of the generative force to mould matter to its will.

Views on Conception

In his view of conception we have evidence of the sheer delight which Harvey takes in allowing his imagination to range in the realms of the immaterial. He finds much "to admire and marvel at in conception. It is a matter, in truth, full of obscurity; yet will I venture to put forth a few things—rather though as questions proposed for solution." He returns to his demonstration at an earlier stage that the woman is "fecundated without the co-operation of any sensible corporeal agent, in the same way as iron touched by the magnet is endowed with its powers. . . . When this virtue is once received the woman exercises a plastic power of generation, and produces a being after her own image." He then proceeds to repeat the description of the changes in the uterus as he had "found them by observation" in the various animal species which he had dissected. "Its inner surface, the future residence, that is, of the conception, becomes softer, and resembles in smoothness and delicacy the ventricles of the brain."

Then there is for him the grand and inevitable conclusion that "since the substance of the uterus, when ready to conceive, is very like the structure of the brain, why should we not suppose that the function of both is similar? . . . For the functions of both are termed 'conceptions,' and both, although the primary sources of every action throughout the body, are immaterial, the one of natural or organic, the other of animal actions." It is important to recognize that the term "animal" here refers to the function of the "anima"—the mind or, rather, the soul. It is in pushing home his argument that Harvey here makes use for the first and only time of the syllogism in the true scholastic manner. Let A stand for the fertile egg or the "material cause" of the chick and B for that which fecundates the egg—that is, the "efficient cause" of the chick. Let C be the chick itself—that is, the "final cause" or the immaterial "form" or "species," the reason why the chick is. Whenever B exists C also exists. Whenever A exists B also exists. Therefore whenever A exists C also exists. From this we may conclude that "the 'species' or immaterial 'form' of the future chick are, in some sort, the cause of the impregnation or fecundation of the uterus, because after intercourse no corporeal substance can be found within that organ." Here, in his employment of the various "causes" and of the immaterial "species" or "form," Harvey reveals himself as the true Aristotelian.

While we may thus in humility, and hence with understanding, accompany a great mind in the passionate and yet unavailing struggle towards the truth, we cannot help, from our privileged position, recalling the criticism, quoted earlier, which Harvey levels against the "erroneous and almost foolish" methods of those by whom "single universal conclusions being deduced from several premises, and analogies being thence shaped out, we have frequently mere verisimilitudes handed down to us instead of positive truths."

Harvey's Mysticism

We have seen how the stars enter into the processes of generation. But the full import of these beliefs is revealed when Harvey deals with the blood. Here we come face to face in fullest measure with the mysticism that enters so largely into Harvey's attitude to nature. His descriptions of the blood are suffused with a remarkable glow, and we come upon Harvey as the poet transported into the empyrean by the sheer passion of his contemplation of the divine made flesh. To quote: "The blood, therefore, by reason of its admirable properties and powers, is 'Spirit.' It is also celestial; for nature, the soul, that which answers to the essence of the stars, is the inmate of the spirit, in other words, it is something analogous to heaven, the instrument of heaven, vicarious of heaven." Here we have a further glimpse of the cosmic order in which Harvey believed. Again: "Contained within the veins, however, inasmuch as it is an integral part of the body, and is animated, regenerative, and the immediate instrument and principal seat of the soul, inasmuch, moreover, as it seems to partake of another more divine body, and is transfused by divine animal heat, it obtains remarkable and most excellent powers, and is analogous to the essence of the stars. In so far as it is spirit, it is the hearth, the vesta, the household divinity, the innate heat, the sun of the microcosm, the fire of Plato."

The primacy of the blood is established by the fact that it is the first part of the animal to be formed. "We are to reject the views of certain physicians, indifferent philosophers, who will have it that three principal and primogenate parts arise together, viz.: the brain, the heart, and the liver; neither can I agree with Aristotle himself, who maintains that the heart is the first engendered and animated part; for I think that the privilege of priority belongs to the blood alone. . . . There appears at first, I say, a red-coloured pulsating point or vesicle . . . and, in so far as we are enabled to perceive from the most careful examination, the blood is produced before the punctum saliens is formed." The supremacy of the blood is further apparent from the observations that the pulse is derived from it, for "the diastole . . . takes place from the blood swelling, as it were, in consequence of containing an inherent spirit." The action of the heart is "produced by a double agent: first, the blood undergoes distension or dilatation, and secondly, the vesicular membrane of the embryo in the egg, the auricles and ventricles in the extruded chick, effect the constriction." In other words, the dominant element in the heart's action is the diastole produced by the swelling of the blood by virtue of its innate heat; the systole is the muscular recoil.

Harvey is at great pains to show that the blood is from the beginning endowed with its superlative powers and that thereafter it is self-sufficing and independent of the elements. It is, or possesses, the "animal heat, in so far, namely, as it is governed in its actions by the soul; for it is celestial as subservient to heaven; and divine, because it is the instrument of God the great and good."

A Comparison in Philosophies

Sherrington (*Man on His Nature*, Cambridge University Press, 1946) has recently published a sympathetic study of Fernel, the great French doctor-philosopher, who lived a century before Harvey and whom Harvey quotes once in *De Generatione*. This analysis invites a comparison between the philosophies of the two men, from which we get a forcible impression of the similarity of their views despite their wide separation in time. In his general conception of the cosmic order and its relation to the operations of the animal body, in his preoccupation with the stock-in-trade of the ancient philosophers, the souls and causes and forms, the innate heat and the immaterial elements in nature, Harvey has much in common with his illustrious predecessor. But, whilst in Fernel authority still retained a supreme place, there is in Harvey a novel urge to test each fact by direct observation. Nevertheless it is clear that the mediaeval still had its firm hold on the mind of our great countryman, who is presented through his works as a kind of dual personality—an epitome, as it were, or reflection of the conflict in loyalties that belonged to the period of great transition in which he lived.

We have clear evidence that Harvey had a strong element of reaction within his nature. We have seen that he allowed the revolution of cosmological thought to pass him by. There is a measure of irony in the fact that in his contempt for "matter" and of the "chymists," who trafficked in "matter," he of necessity remained aloof from the increasing interest being taken in the inner structure and properties of matter, by which his own problems were alone to find their solution. But for him the "chymists" were in the main mere dishonest alchemists and sorcerers, and it was still to be some time before Boyle established the repute of the chemist, and a considerable time was to elapse before Black was to throw light on the source of animal heat.

But in some ways we find the greatest irony of all in the fate of his discovery of the circulation of the blood. We have already alluded to the fact that Descartes was one of Harvey's early converts. He employed Harvey's descriptions in his argument that the animal body is to be regarded as a complex machine. In his *Discourse on Method* (1637) he reproduces Harvey's account of the circulation and argued by analogy that, as the blood tubes carry a vital fluid, the nerves, distributed throughout the body on a similar pattern, must be tubes conveying a fluid to the brain with sensations and from the brain for muscular action. It is true that Descartes himself regarded the body "as a machine made by the hands of God," but it is nevertheless the case that his views were in the end to usher in the materialism of the eighteenth century. Thus, whilst Harvey was describing the blood, with its celestial powers, as the "sun of the microcosm," Descartes was explaining the circulation and the bodily functions in terms of physics. We thus have the spectacle of Harvey's own work largely contributing, in the early seventeenth century, to the final replacement of the Solar deity within the microcosm by a rigid mechanism, just as, later in the century, Newton, following Kepler and Galileo, established the rule of mechanical law in the macrocosm. Harvey has his share in the final collapse of the Ptolemaic system and its celestial ministrations, in which he fervently believed.

It has sometimes been maintained that the highly speculative nature of much of the *De Generatione*, resulting in conclusions often subsequently overthrown, argues the work of an ageing man. The book was, it is true, published in 1651, when Harvey was 73 years old, but there is good evidence that he was actively engaged in his studies even before the appearance of his *De Motu* in 1628. Indeed, some remarks in the *De Motu* suggest that he had reached several of his main conclusions before that date.

The Speculations of Genius

The difference in the standards of lasting achievement in Harvey's two works is more convincingly to be found, as we have already suggested, in the nature of the respective studies. They were the work of the same keen mind, of the same keen imagination, but from the nature of things they differed in the degree in which theory was based upon reliable observations. In the one the data were there both to inspire and to "prove" the theory; in the other they were at that era beyond the ken of man. As Harvey, himself conscious of the scepticism which he was sure to meet, says in his chapter on conception: "Yet this I do is the practice of philosophers who, when they cannot clearly comprehend how a thing really is brought to pass, devise some mode for it in accordance with the other works of nature, and as near as possible to what is true. And indeed all those opinions, which we now regard as of the greatest weight, were at the beginning mere figments and imaginations, until confirmed by experiments addressed to the senses."

Were it possible it would still be unprofitable to seek to restrain the speculations of genius. Descartes, possessing kinship to Harvey both in outlook and in time, would suffer heavily under such a charge, for did he not explain the universe in terms of a vortex theory, and did he not place the rational soul in the pineal gland? Many of the speculations of the greatest philosophers and scientists have suffered badly at the hands of time.

Both in his work on generation and in that on the circulation Harvey found it necessary to invoke the influence of the stars. In the former we are at the end largely left with the stars so far as its major themes are concerned. In the latter the blood is "the sun of the microcosm" and the stars are still in control, but the mechanism by which this celestial influence achieves its purpose is revealed to us. The Harveian method, with its grand synthesis of the searching eye and the comprehending mind, unlocks for us the secret and places medical science for ever in its debt. The climax of discovery is almost hidden in the simplicity of its statement: "Coepi egomet mecum cogitare, an motionem quandam quasi in circulo haberet, quam postea veram esse referi" (I began to think whether there might not be a motion, as it were, in a circle; this I later found to be true).

According to a recent report in the *New York Times*, experiments on the preservation of food by atomic radiation are now in progress at the University of Michigan. Homogenized pasteurized milk was sealed in plastic bags and exposed to the radiation from radioactive Co^{60} for 24–40 hours. After three weeks at room temperature (77° F.—25° C.) it was still more or less normal, while control samples, also in plastic bags but not irradiated, turned sour in 24 hours. Likewise beef bought locally kept fresh for three weeks after irradiation, whereas controls were bad in 48 hours. Experiments have also been made with fruit and vegetables, but so far without satisfactory result.

BLOOD CHOLINESTERASE LEVELS AND RANGE OF PERSONAL VARIATION IN A HEALTHY ADULT POPULATION

BY

S. CALLAWAY, B.Sc.

D. R. DAVIES, M.Sc., F.R.I.C.

AND

J. P. RUTLAND

(From the Ministry of Supply, Porton)

The power to inhibit cholinesterase is shared by a number of chemical compounds now in use as insecticides, while others have been proposed for use in chemical warfare. When absorbed by the body all these compounds may produce a significant reduction in the level of the red-cell or plasma cholinesterase before symptoms of systemic poisoning become evident. For this reason information about the level of these enzymes in the blood of any individual will be of value in helping to decide whether or not he or she has absorbed any of these materials. Further, recovery from the effects of poisoning can be considered to be complete only when the blood cholinesterase has returned to normal levels.

Until normal limits and variations for blood cholinesterase levels have been determined, it is obviously impossible to decide whether or not an individual has or has not got a normal blood cholinesterase level at any given time.

The present work consists of a detailed analysis of the results of determining cholinesterase levels, both in plasma (" pseudo "-cholinesterase) and in red blood cells (" true " cholinesterase). In all, 247 healthy adults drawn from the armed Services and the civilian population have been examined. The limits of personal variation have been based on a series of eight successive determinations made at fixed intervals on ten healthy men.

Technique

Blood obtained by venepuncture was collected in ammonium and potassium oxalate (10 mg. per 5–10 ml. blood). The blood was centrifuged for 10 minutes at 500 *g* and the cells were washed twice with 0.85% NaCl, the final spinning being for 20 minutes at 500 *g*.

For the determination, 0.2 ml. of the plasma or packed cells was added to 11.8 ml. of distilled water, and 2 ml. of this dilution was used for analysis. The cells or plasma were added to 0.5 ml. of 0.12 M sodium bicarbonate in a Warburg vessel to which 0.5 ml. of a solution of acetylcholine had been added to the side arm. For analysis of the red cells 0.036 M solution of acetylcholine was used, and for the plasma a 0.36 M solution. Such preparations from normal blood produced an output of approximately 100 microlitres of CO_2 in 30 minutes at 38° C. The flask and contents were gassed for 10 minutes with a mixture of 95% nitrogen and 5% carbon dioxide in the Warburg bath at 38° C. The acetylcholine was then tipped into the well of the flask. After an interval of ten minutes for the temperature to reach equilibrium, manometer readings were taken every 15 minutes for one hour and the results calculated by the method of Aldridge, Berry, and Davies (1949). The unit of enzyme activity was defined as the amount of enzyme contained in 1/30 ml. of cells or plasma which would produce one microlitre of carbon dioxide in 30 minutes.

Because of the inevitable delays between the taking of a blood sample and its arrival in the laboratory for examination, it was important to know what effect this would have on the enzyme levels in the cells and plasma. A large pooled sample of human blood was divided into two parts. One was retained as whole blood and maintained at room temperature. The other part was separated into plasma and red cells and kept at 0° C. Samples of each were examined daily for five days. The results are given in Table I.

TABLE I.—*Effect of Storage of Whole Blood, Plasma, and Red Cells Upon Cholinesterase Activity*

Time in Days	Cells and Plasma Stored at 0° C.		Whole Blood Stored at Room Temp.		Remarks
	Cells	Plasma	Cells	Plasma	
0	—	—	131	102	
1	136	102	132	104	
2	132	99	124	103	Haemolysis
3	134	100	122	106	,,
4	132	100	118	110	,,
5	137	99	90	124	Marked haemolysis

It will be seen that the activity of whole blood at room temperature is maintained for 48 hours, but with the onset of visible haemolysis the value of the red-cell enzyme decreases while that of the plasma increases. If the cells and plasma are separated and stored at 0° C. the cholinesterase content of each remains constant for at least five days.

Results

1. Variations in Plasma and Red-cell Cholinesterase in a Healthy Adult Population

The value of any estimate of the variation of blood constituents in health depends as much upon the accuracy with which the assessment of health is made as upon the precision with which the chemical analyses are carried out. The problem is as much statistical and demographic as analytical.

Data have therefore been obtained from three groups, each of which is further subdivided into a summer (August–September) group and a winter (November–March) group, and each of which is carefully defined with reference to its standard of health and sociological nature. The details are given in Table II.

TABLE II.—*Source and Nature of the " Normal " Groups Examined*

Group	Period of Observation	Source	No. in Group	Characteristics of Group
I*a* I*b*	Nov.–Dec., 1949 Aug.–Sept., 1950	R.N., Army, and R.A.F.	68 32 } 100	Males aged 18–30. All fit for combat duty everywhere
II*a* II*b*	Jan.–Mar., 1950 Aug.–Sept., 1950	Civil pop. of S.W. England, urban and industrial	52 29 } 81	Males aged 18–69. No history of serious illness for at least two years
III*a* III*b*	Jan.–Mar., 1950 Aug.–Sept., 1950	As II*a* and II*b*	53 13 } 66	Females aged 25–74. History as II*a* and II*b*

The first group consisted of 100 men aged 18–30 from the armed Services, each designated as " fit for full combat duty anywhere " (Service group). The second group

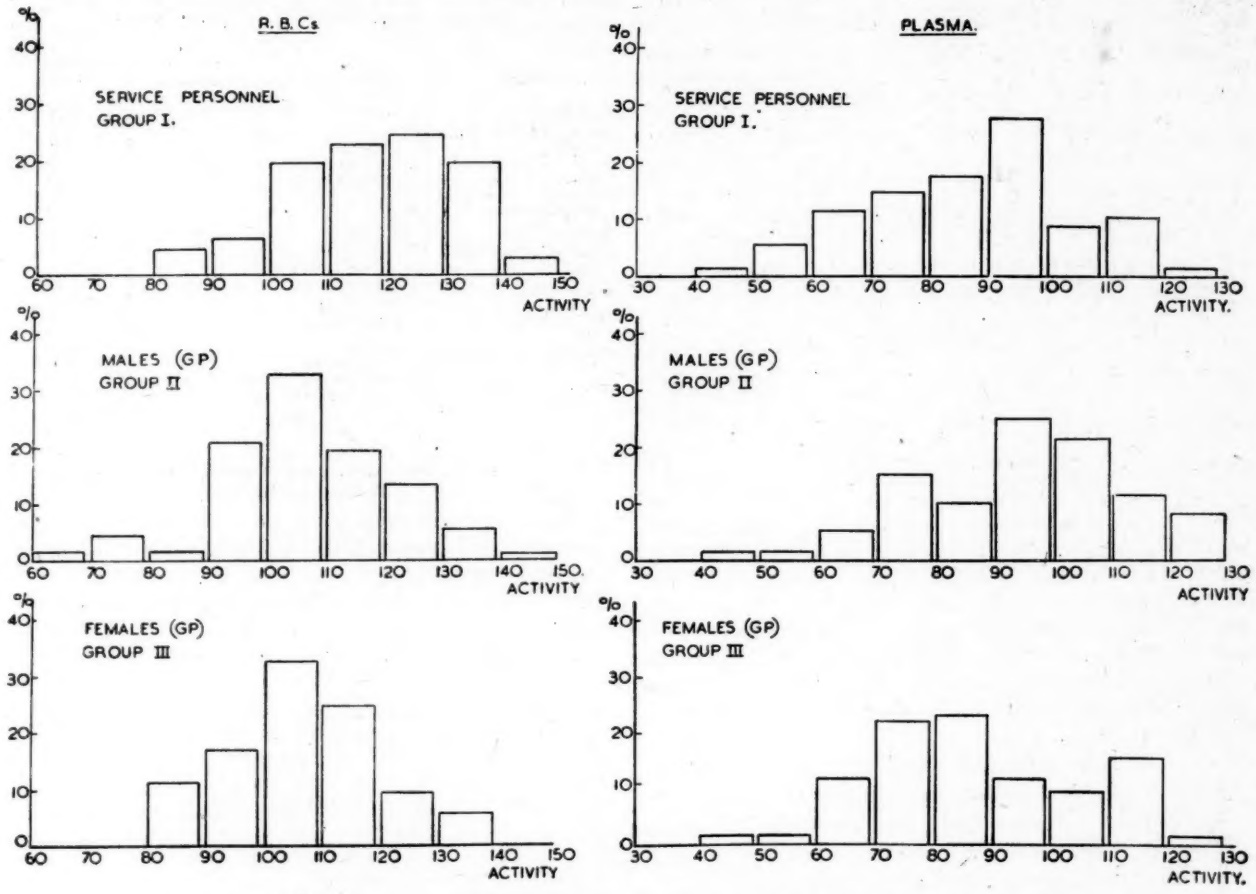


FIG. 1.—Distribution and activity diagrams showing levels of plasma and red-cell cholinesterase.

consisted of 81 men aged 18–60 from South-west England, and the third group consisted of 66 women aged 25–74 (civilian groups).

No member of the last two groups gave a history of any serious illness within the preceding two years, and as they were all blood donors they could be considered to be free from the common infectious diseases at the time the blood was taken.

Distribution–activity diagrams for the level of both the plasma and the red-cell enzyme in all three groups have been constructed. They show (Fig. 1) that the distributions do not depart significantly from normal, but the mode of the red-cell enzyme distribution occurs at a higher level of activity in Group I (Service group) than in either of the civilian groups.

In Table III the means with standard deviations for the level of each enzyme in all groups are given, and the figures show that there is no significant difference between the mean values of the plasma enzyme in any group, while the mean value of the red-cell enzyme is significantly higher in the Service group. There is no difference between the mean values of the male and female groups of the civilian population.

TABLE III.—*Comparison of Plasma and Red-cell Cholinesterase in Healthy Persons*

Group	No.	Mean	Stand. Dev.	Significance	
Plasma:					
Service	87	86·7	17·0	P>0·05	P>0·05
Civilian males ..	76	90·6	24·6		
Civilian females ..	65	88·3	20·6	P>0·05	
Red cell:					
Service	96	117·7	12·7	P<0·05	P<0·01
Civilian males ..	79	109·6	16·4		
Civilian females ..	65	107·7	12·8	P>0·05	

The difference between the red-cell enzyme level in Group I and that in Group II cannot readily be explained except possibly on the higher level of physical fitness that might be expected in the Service group.

Age does not influence the level of either enzyme in the adult (Fig. 2), and a comparison of the Service group with a group of civilian males of the same age showed that the former still had a significantly higher level of red-cell enzyme.

No seasonal differences were observed. The mean value of the plasma enzyme during the summer was 87.1 (s.d. 20.6). During the winter it was 90.0 (s.d. 19.1). This difference is not significant ($P>0.05$). The significant difference between Service and civilian red-cell values necessitates a separate comparison. The mean red-cell cholinesterase for the Service group was 116.4 (s.d. 11.0) during the summer and 118.2 (s.d. 13.9) during the winter; ($P>0.05$). The comparable figures for the civilian group were 110.9 (s.d. 16.2) and 107.9 (s.d. 14.2); ($P>0.05$).

These figures incidentally serve as a control of the method and indicate that the results obtained at different times are strictly comparable.

The limits of variation based on a 95% level of probability have been determined for the plasma enzyme level in the whole population examined, and for the

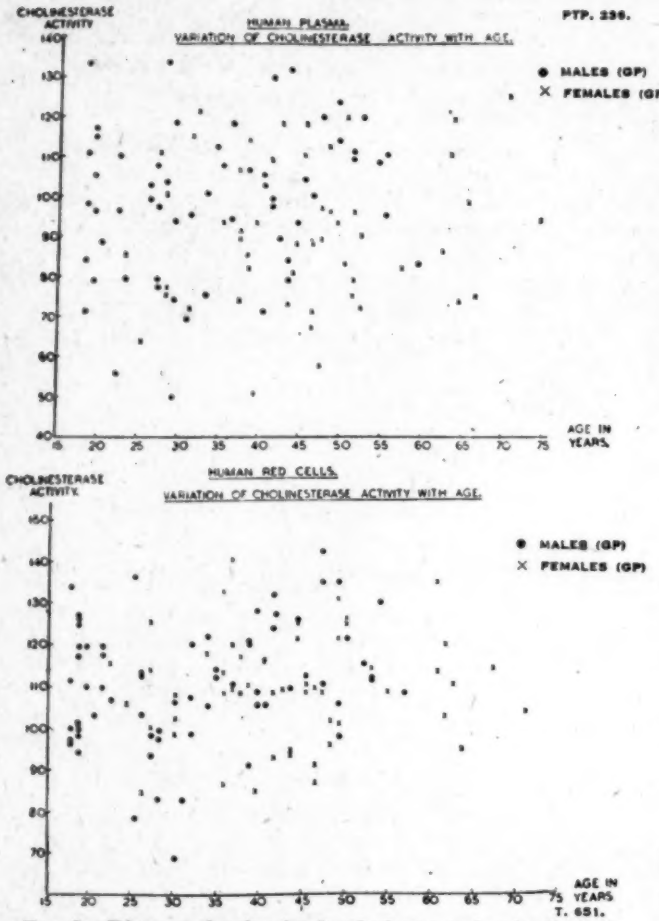


FIG. 2.—Diagram showing levels of plasma and red-cell cholinesterase according to age.

TABLE IV.—*Limits of Variation in Cholinesterase (ChE) Levels in the Red Cells and Plasma of Adults*

Enzyme	Group	No.	Mean (ChE Units)	Stand. Dev. (ChE Units)	Limits (ChE Units)
Plasma ..	All groups	228	89·3	19·4	51–128
Red cell ..	Service	98	117·7	12·7	92–143
	Civilian	145	108·2	16·7	75–142

red-cell enzyme for the Service and civilian groups. If the mean value of the enzyme activity is expressed as 100, and the standard deviation as a percentage standard deviation—i.e., the coefficient of variation—the limits can then be expressed in a more universally applicable form.

TABLE V.—*The Coefficient of Variation of Plasma and Red Cell. Mean = 100*

Enzyme	Group	Coefficient of Variation	Limits
Plasma	Total	21·7	57–143
Red cell ..	Service	10·8	78–122
	Civilian	15·4	69–131

Using the coefficient of variation, it is possible to compare the results from experiments done by different techniques. The results of others have been calculated in this way and comparisons made. These are summarized in Tables VI and VII. With the exception of the continuous titration technique there is remarkably good agreement in the coefficient of variation of the results from the use of different methods.

TABLE VI.—*A Comparison of "Normal" Limits of Plasma Enzyme as Determined by Various Authors*

Author	Technique	No. of Observations	Coefficient of Variation
Present paper ..	Warburg: substrate acetylcholine	141	22·8
Levine and Hoyt (1949)		66	20·4
		67	18·9
Michel (1948) ..		80	22·5
		42	21·5
Callaway and Davies (unpublished)		11	18·1
Wilson (1949) ..	Warburg: substrate benzoylcholine	100	28·5
Davies and Rutland (1950)		49	25·8
Davies and Rutland (1950)	Electrometric: substrate acetylcholine	47	24·5
Michel (1949) ..		42	21·4
Piccoli and Longo (1947)	Continuous titration: substrate acetylcholine	30	12·5
Meyer *et al.* (1948) ..		15	30·2

2. Variation in the Red-cell and Plasma Cholinesterase in a Healthy Individual

Blood samples were taken on eight occasions over a period of four weeks from ten soldiers aged 18–30, each engaged on normal service duty. The mean plasma cholinesterase, with its variation, is given for each individual in Table VIII. The overall mean is 89.0 and the average variance is 58.6. It is necessary to consider

TABLE VII.—*A Comparison of "Normal" Limits of Red-cell Enzyme as Determined by Various Authors*

Author	Technique	No. of Observations	Coefficient of Variation	
Present paper ..	Warburg: substrate acetylcholine	98	10·7	Service group
Callaway and Davies (unpublished)		27	12·3	Civilian group
Present paper ..		145	15·4	
Wilson (1949) ..	Warburg: substrate acetylmethylcholine	100	12·5	Civilians
Davies and Rutland (1950)		50	15·4	,,
Davies and Rutland (1950)	Electrometric: substrate acetylcholine	48	15·9	,,
Meyer *et al.* (1948) ..	Continuous titration: substrate acetylcholine	15	10·2	

whether this variance is homogeneous or whether it is an average of variances which differ widely from subject to subject.

TABLE VIII.—*The Homogeneity of the Personal Variation of Plasma Cholinesterase*

Subject	Mean ChE	Variance	Stand. Dev.
A	86·1	49·3	7·0
B	95·0	19·7	4·4
C	89·4	37·1	6·1
D	101·5	69·2	8·3
E	84·1	97·0	9·9
F	73·2	63·4	8·0
G	100·0	83·7	9·1
H	90·2	66·7	8·2
J	84·4	23·4	4·8
K	86·2	76·8	8·8

Bartlett's (1937) test for the homogeneity of these variances provides a value for χ^2 of 8.0 with $P=0.54$. Although the variances range from 19.7 to 97.0, with corresponding standard deviations of 4.4 to 9.9, their average values of 58.6 and 7.6 respectively may be considered to be the best estimate of the personal variation of the plasma enzyme.

The essential purpose of this paper is to facilitate the recognition of abnormal values of cholinesterase with the minimum of observations on the normal. This problem may be stated in more precise terms as follows:

1. If a single estimate of the enzyme is available, what must be the difference between this and a second estimate for the latter to differ significantly? Such differences between observations which have been derived from a single population with variance σ_1^2 are distributed normally about zero mean with variance $\sigma^2=2\sigma_1^2$. An estimate of σ_1^2 is given above—viz., 58.6—and thus σ^2 becomes 117.2 and the standard deviation 10.8.

Since it is intended to use the information resulting from this inquiry to investigate processes involving the inhibition of cholinesterases, only negative values of such differences are of interest. In consequence, the appropriate multiplier of the standard deviation for 5% significance is 1.64. Thus the second result must be 17.7 units below the first.

2. Similarly, if two such estimates, x_1 and x_2, are available, what must be the difference between the mean of these two and a third, x_3? Here again the distribution of such differences must be considered. If the mean of the first two estimates be regarded as the equivalent of the initial estimate of the previous example the same treatment is applicable, but here the variance of this mean is $\sigma_1^2/2$. Thus, the difference will be distributed normally around zero mean with variance $3\sigma_1^2/2$.

3. Similarly, with three initial estimates, the difference between their mean and a fourth estimate will be distributed normally about zero mean with variance $4\sigma_1^2/3$.

On this basis an instructive table (Table IX) has been drawn up in which the value of such significant differences has been calculated for a varying number of initial estimations.

TABLE IX.—*Minimum Differences for the Recognition of Abnormal Personal Red-cell and Plasma Cholinesterase Values*

No. of Initial Estimations	Standard Deviation of Difference of Suspected Observation from Mean	Significant Difference 1·64
1	$\sigma\sqrt{2} = 10{\cdot}8$	17·7
2	$\sigma\sqrt{3/2} = 9{\cdot}4$	15·4
3	$\sigma\sqrt{4/3} = 8{\cdot}8$	14·5
4	$\sigma\sqrt{5/4} = 8{\cdot}5$	14·0
5	$\sigma\sqrt{6/5} = 8{\cdot}4$	13·8
10	$\sigma\sqrt{11/10} = 8{\cdot}0$	13·1
	$\sigma = 7{\cdot}6$	12·6

The red-cell data have been accorded a similar treatment, and the results are recorded in Table X.

TABLE X.—*The Homogeneity of the Personal Variation of Red-cell Cholinesterase*

Subject	Mean ChE	Variance	Stand. Dev.
A	122·5	100·3	10·2
B	105·8	52·2	7·2
C	108·9	17·9	4·2
D	120·3	53·6	7·3
E	113·0	74·3	8·6
F	107·5	69·7	8·3
G	129·4	25·7	5·1
H	118·8	74·2	8·6
J	112·1	53·6	7·3
K	117·4	62·3	7·9

Bartlett's test for the homogeneity of variances yields from the above data a value for χ^2 of 7.2 with 9 degrees of freedom ($P=0.62$). Thus, although the variances range from 17.9 to 100.3, with corresponding standard deviations of 4.2 to 10.2, the average values of 58.4 and 7.6 respectively may be accepted as the best estimates of personal variation.

The rather unexpected result has emerged that the average personal variance is numerically identical in both plasma and red-cell enzyme; thus the significant differences given in the third column of Table IX are applicable to the plasma enzyme.

Using the present data, an average value for the coefficient of variation can be calculated, and on the basis of a mean value of 89 for the plasma enzyme and 115.6 for the red-cell enzyme the respective coefficients are 8.5 and 6.6. These values may be used for the construction of a table similar to Table IX wherein column 3 will give percentage differences only. Such a table (Table XI) would be applicable to any other technique of analysis provided that sufficient data are available to permit the calculation of a mean to which these coefficients may be related.

TABLE XI.—*Percentage Minimum Differences for the Recognition of Abnormal Red-cell and Plasma Cholinesterase Values*

No. of Initial Estimations	Percentage Differences	
	Plasma	Cells
1	19·9	15·3
2	17·3	13·3
3	16·3	12·5
4	15·7	12·1
5	15·5	11·9
10	14·7	11·3
	14·1	10·9

Discussion

On the basis of a large number of results from a healthy adult population it has been possible to lay down limits between which the normal levels of red-cell and plasma cholinesterase will lie. Sex, age, occupation, and season are without effect upon the level of the plasma enzyme. But in the case of the red-cell enzyme a group of Service men were found to have a significantly higher mean level than a male civilian population of comparable age. It is conceivable that this may be due to the active outdoor life led by all of the first group together with a high general level of physical fitness.

The level of cholinesterase has a normal distribution among the adult population. If the variations are expressed as coefficients of variation rather than as standard deviations for the results of a particular method, it is possible to compare the results obtained by workers using different techniques. But, it need hardly be added, each worker must establish a satisfactory means for his own results.

It is thus possible to take a sample of blood from an individual and say whether or not the plasma or red-cell enzyme level lies within normal limits. However, the range of these limits is rather great, and further work was done to establish the limits for an individual's variation in the level of either enzyme when estimates were made at different times.

It was found that the range of these limits was considerably smaller than that of the whole population. This means that, where an individual is exposed to an inhibitor of cholinesterase and absorbs some of it, the level of cholinesterase in his cells or plasma may be significantly depressed below his own normal level and yet this new low level may be within the limits of normality for the population as a whole.

If it is possible to make only a single estimation from individuals exposed to these compounds, then it can be

said whether or not their level falls outside the normal range, and if it is below normal it is good evidence that they have absorbed some of the inhibitor. Fortunately, the lower normal level of the population is well above the highest level at which symptoms of systemic poisoning are likely to become apparent.

If, however, two successive samples of blood can be taken over a period during which the individual was exposed to these compounds, or over a period immediately following such an exposure, it might be possible to show that the variations of his individual levels varied beyond the range of his personal normal level and indicated absorption of a cholinesterase inhibitor.

The limits have been accurately defined and the degree of significance of the variations has been described.

A more universal application of the technique will await the development of methods less complicated than the one used in this work and the adoption of these newer techniques as a routine method in chemical pathological laboratories.

Summary

The variations in plasma and red-cell cholinesterase have been determined in a large group of 247 healthy adults drawn from the armed Services and civilian population.

Limits of variation have been defined for the plasma enzyme for the whole sample, but separate limits were necessary for the red-cell enzyme from the civilian and Service groups. These limits lie between 57 and 143% of the mean value for the plasma enzyme and 78 and 122% of the mean red-cell enzyme value for Service personnel. The corresponding limits for the red-cell cholinesterase for civilians are 69 and 131% of the mean.

There were no sex, age, or seasonal differences in either enzyme.

It has been shown that the coefficient of variation is a valuable index for defining the limits of variation in both enzymes.

The personal variation has been studied in 10 soldiers by examining blood samples upon eight separate occasions.

It has been possible to make estimates of the fall in enzyme level necessary to indicate departure from the normal. This value varies with the number of initial observations, but is numerically the same (in enzyme units) for both plasma and red-cell enzymes.

A knowledge of the results here presented permits the early recognition of abnormal levels of red-cell and plasma cholinesterase.

We are greatly indebted to Surgeon Commander W. H. McKee, R.N., and to Dr. R. S. Tovey, Director of the South-western Region Blood Transfusion Service, for supplying us with blood samples. We wish also to thank the Service and civilian personnel who co-operated in this inquiry. Finally, we wish to record our appreciation of the careful and accurate assistance we have received from Miss A. M. Eyres and Corporal E. Kerr, R.A.M.C. Acknowledgment is made to the Chief Scientist, Ministry of Supply, for permission to publish this paper. Crown copyright reserved. Reproduced with permission of the Controller of H.M. Stationery Office.

REFERENCES

Aldridge, W. N., Berry, W. K., and Davies, D. R. (1949). *Nature, Lond.*, **164**, 925.
Bartlett, M. S. (1937). *J. roy. Statist. Soc.*, Suppl. **4**, 137.
Davies, D. R., and Rutland, J. P. (1950). *Biochem. J.*, **47**, xxi.
Levine, M. G., and Hoyt, R. E. (1949). *Proc. Soc. exp. Biol., N.Y.*, **70**, 50.
Meyer, L. M., Sawtisky, A., Ritz, N. D., and Fitch, H. M. (1948). *J. Lab. clin. Med.*, **33**, 189.
Michel, H. O. (1948). *Med. Div. Inf. Prog. Rep.*, July, p. 38.
—— (1949). *J. Lab. clin. Med.*, **34**, 1564.
Piccoli, R., and Longo, G. (1947). *Boll. Soc. ital. Biol. sper.*, **23**, 356.
Wilson, A. (1949). Unpublished Prog. Rep. to Ministry of Supply.

BLOOD CHOLINESTERASE LEVELS IN WORKERS EXPOSED TO ORGANO-PHOSPHORUS INSECTICIDES

BY

J. M. BARNES, M.B., B.Ch.
Medical Research Council Toxicology Research Unit, Carshalton

AND

D. R. DAVIES, M.Sc., F.R.I.C.
Ministry of Supply, Porton

During the last twelve months several reports have appeared which emphasize the toxic properties of a group of substances commonly referred to as the organo-phosphorus insecticides (Report to Pesticides Committee, 1950; Goldblatt, 1950; Bidstrup, 1950; Grob *et al.*, 1950). At least 30 fatalities have occurred among workers handling these compounds in America (Abrams *et al.*, 1950). No fatal cases of poisoning have occurred in Great Britain, and only a single non-fatal case has been reported (Milles and Salt, 1950). A working party has been set up by the Ministry of Agriculture to consider the various problems that arise in connexion with the use of toxic chemicals in agriculture. Its report and recommendations are awaited.

These organo-phosphorus insecticides are valuable adjuvants to modern agricultural practice. It is obvious that, like any other poisonous compounds, they can be handled only if suitable safe techniques can be devised. One very important safety procedure would be the development of a clinical test that would make it possible to detect the absorption of the poisons before enough had been taken in to produce a dangerous or fatal intoxication.

All the organo-phosphorus compounds used as insecticides have one common property. When they are introduced into the body they inhibit the enzymes that hydrolyse acetylcholine. In man both the "pseudo" and the "true" cholinesterase circulate in the blood; the former is found in the plasma and the latter in the red blood corpuscles. Furthermore, observations by one of us (D. R. D.) on animals have shown that the amount of these enzymes circulating in the blood may be lowered by at least 80% without symptoms of poisoning (due to the accumulation of acetylcholine) appearing.

Since techniques for measuring the level of cholinesterase in the blood are available, a determination of the cholinesterase level at any given time could be used to decide whether the poison was being absorbed even in quantities too small to produce symptoms of poisoning. Garlick (1950) has already emphasized the value of blood cholinesterase determinations to those responsible for the medical care of workers exposed to these insecticides during their manufacture.

Ideally, a series of determinations of the blood cholinesterase should be done on any individual before, during, and after exposure to the insecticides, whether in the factory or in the field. Callaway *et al.* (1951) have determined the range about which the level of a normal individual may vary, and so it would not be possible to say in any individual case whether or not a reduction

in the level of cholinesterase below the level found before exposure was significant and therefore most probably due to absorption of the insecticide. The individual could then be removed from further contact until his cholinesterase level had returned to normal. Grob *et al.* (1947) have shown that the complete restoration of the blood cholinesterase levels in man is comparatively slow.

It is possible to carry out regular cholinesterase determinations on the same individual with little inconvenience to the worker if the modification of Davies *et al.* (1951) to the method of Michel (1949) is employed, using only a drop of blood.

The observations to be described in this paper were made with the technique described in the preceding paper (Callaway *et al.*, 1951) upon plasma and washed red cells. For this purpose a sample of blood had to be obtained by venepuncture. Because of the difficulties of obtaining repeated samples from the workers concerned, only single observations were made in the great majority of cases.

Callaway *et al.* (1951) have determined the range of blood cholinesterase levels for two healthy adult populations and also the range of variation in the level of healthy Service personnel on whom separate determinations were made at different times. It is the existence of these data which has imparted significance to the observations made in this paper.

Materials and Methods

Examination has been made of 130 specimens of blood from 80 men and women who have been exposed to these insecticides in field or factory. These workers were civilians whose ages ranged from 17 to 59, and it is therefore appropriate that the cholinesterase levels observed among this group should be compared with the values for a mixed civilian population rather than the higher levels of the Service personnel group (see Callaway *et al.*, 1951). The specimens were obtained from 30 factory and 50 agricultural workers. The factory workers were employed at three separate factories. The agricultural workers came from orchards in Essex, Sussex, and Worcester, together with a number of men employed on contract spraying in parts of Kent and East Anglia.

The factory workers included both those packing or preparing concentrated materials and also laboratory workers in contact with a number of different active compounds. The majority of the field workers were farm employees doing fruit-spraying as one of their normal activities. All of them had been working for at least two days continuously with the insecticides before their blood was examined. (The normal period of spraying with this type of worker was never more than three to four days continuously.) Only a few of these men come into contact with the concentrated materials, as one man would act as the mixer for a large group applying the spray.

All the field workers and the majority of the factory workers were exposed to insecticides containing either "parathion" (main active principle, 0.0-diethyl-*para*-nitrophenyl-thiophosphate) or "schradan" (active principle, octamethyl-pyrophosphonamide). A few factory workers were exposed to other compounds in the laboratories of the factory concerned.

Blood was collected, either during or at the end of a working day in the field or factory, in a Behring venule containing oxalate. All specimens were sent through the post to a central laboratory, where enzyme analyses were made. There was an inevitable delay of at least 24 hours between taking the blood and the estimation of cholinesterase. This delay was, however, unimportant, since it had previously been shown (Callaway *et al.*, 1951) that the levels in stored blood are unaltered over a period of at least five days, so long as the red cells and plasma are separated before the onset of haemolysis. Under normal conditions of storage even at atmospheric temperatures no significant haemolysis takes place within the first four days in oxalated blood. It is important, therefore, to note whether or not haemolysis has taken place in any specimen of blood where there has been a delay between the time of its collection and the determination of the cholinesterases.

Determinations of plasma and red-cell cholinesterase were made by the method described by Callaway *et al.* (1951). The values of red-cell and serum cholinesterase are expressed in units of enzyme, one unit being the amount of enzyme present in 1/30 ml. of cells or serum which produces one microlitre of carbon dioxide in 30 minutes.

Results

Callaway *et al.* (1951) have found that the red-cell cholinesterase levels of a healthy civilian population will fall between the range of 75 and 142 units. The chances of a healthy individual having a red-cell cholinesterase level below 75 units would be 1 : 40.

Of the 80 individuals examined during this investigation three only were found to have levels below 75 units. All were factory workers and therefore liable to come into contact with strong solutions of the insecticide. Only one exhibited any symptoms, and these were mild. Although the reduction in each case was only just below the normal minimal level in the civilian population, the level of the enzyme rose in two of the subjects after their removal from contact with these materials.

It thus seems reasonable to conclude that in at least two individuals the depression of cholinesterase levels of the red blood corpuscles had resulted from the absorption of small quantities of the insecticides to which they were exposed.

TABLE I.—*Red-cell Cholinesterase Levels in Three Male Factory Workers Found to Have Reduced Levels After Exposure to Insecticides*

	Cases		
	L.H.	W.F.	R.N.
Red-cell enzyme (units) immediately after exposure ..	73	69	70
Symptoms	Nil	Nil	Slight tightness of chest
Highest value observed after removal	124	100	—
Estimated rate of regeneration (% per day)	1·0	0·8	—

Normal range, 75–142 units.

Examination of the cholinesterase of the plasma has permitted the recognition of departures from normal levels in five persons, four of whom were laboratory or factory workers, and one a sprayer. The normal lower level of plasma cholinesterase is 51 units. The levels observed in the five cases varied from 44 to 49 units. As in the case of the red cell, the deviation was small but nevertheless quite definite. No symptoms

were observed. This is in keeping with the findings of Mendel, Hawkins, and Nishikawara, who have shown that the plasma enzyme may be inhibited very considerably without the development of symptoms. The results are summarized in Table II.

TABLE II.—*Plasma Enzyme Cholinesterase Levels in Five Insecticide Workers Found to Have Reduced Levels After Exposure*

Case	Enzyme Units	Symptoms	Occupation
F.S.	49	Nil	Sprayer
D.P.	46	,,	Research worker
L.H.*	48	,,	Factory worker
R.N.*	45	,,	,, ,,
E.B.	44	,,	,, ,,

Normal range, 51–127 enzyme units.
* Red-cell enzyme also low.

A third criterion exists for the recognition of disturbances in the normal level of the red-cell or plasma enzymes. It is based upon a knowledge of the limits of the personal variation in the enzyme levels of healthy individuals. The range of these limits and the evidence from which they have been derived are given in the preceding paper (Callaway *et al.*, 1951). In the case of the plasma enzyme a difference of more than 18 units indicates that there has been some abnormal disturbance in the level of this enzyme.

In this inquiry blood specimens were taken on more than one occasion from 14 workers. In eight of these cases the personal variation was greater than normal. The results are presented in Table III. In four cases the level of the enzyme rose in the interval between the determinations. These workers had been removed from contact with the insecticides, and the rise indicated a recovery from the effects of absorption prior to the first determination. In the other four cases contact with the insecticides continued during the interval between the taking of the blood samples. The fall indicated that some absorption of the compounds had taken place though none of the workers developed symptoms.

Thus of the 80 workers examined, 12 showed evidence of absorption of the insecticides with which they had been in contact.

TABLE III

Case	Occupation	Sex	Units of Plasma Enzyme		Difference
			Initial	Final	
(*a*) Cases showing recovery from the effects of previous absorption of insecticide					
F.S.* ..	Sprayer	M	49	76	27
R.B. ..	,,	M	56	83	27
E.B.* ..	Chemical worker	M	44	82	38
H.H. ..	,, ,,	F	51	73	22
(*b*) Cases showing evidence of absorption of insecticide during interval between the determinations					
E.P. ..	Sprayer	M	104	80	24
M.L. ..	Chemical worker	F	99	74	25
J.W. ..	,, ,,	F	79	60	19
C.C. ..	Laboratory worker	F	97	69	28

* Initial values below the normal range.

The estimation of blood cholinesterase was also used as an aid to diagnosis in some instances. The early symptoms of poisoning by these insecticides are mundane in character—headache, dizziness, nausea, abdominal colic, etc. Such symptoms occurring in individuals exposed to these materials would arouse suspicions of poisoning, though similar complaints in unexposed people might be passed over as of no particular importance. A determination of the blood cholinesterase levels would show whether in fact absorption of the insecticide was responsible for the symptoms. In three individuals complaints such as giddiness, abdominal pain, and nausea were made after exposure to insecticides. A determination of the red-cell enzyme showed values in each case practically at the top of the normal range. Absorption of the insecticide was thus excluded. However, local symptoms such as contraction of the pupil and tightness of the chest may result from contact with airborne particles without there being enough absorbed to produce general symptoms or even a detectable reduction in the cholinesterase levels in the blood stream.

Discussion

Slight but statistically quite significant departures from normality have been observed in the levels of blood cholinesterase in 12 out of a group of 80 workers examined during or after exposure to organo-phosphorus insecticides in the factory or field.

Advanced liver disease and severe malnutrition (McCance, 1950) are the only relatively common causes of a depression of the level of blood cholinesterase, and these can be disregarded in considering the population examined during this inquiry.

The results obtained demonstrate effectively the value of blood cholinesterase determinations as part of the medical supervision of workers exposed to the organophosphorus insecticides. In none of the 12 workers showing deviations from normal were there unequivocal symptoms of poisoning, and this can be explained in the light of experiments that have shown that the blood cholinesterase must be depressed to less than 20% of its normal value before symptoms of systemic poisoning appear.

In this inquiry it has been possible to extract information from single determinations of the enzyme levels in individuals. This has been possible only because these results could be compared with data obtained from a large number of determinations from a healthy population.

It is more desirable that a series of determinations should be made on individuals before, during, and after exposure to these materials. Rapid methods requiring only a drop of blood are obviously called for in this kind of work. Such methods do exist, and there is no reason why a sufficiently high standard of accuracy could not readily be reached by any efficient laboratory.

The observations reported here illustrate a number of points. These materials can be handled by field and factory workers without significant absorption taking place. It must, however, be emphasized that the men observed were all told of the poisonous nature of the material they were handling, and, furthermore, that those responsible for the use of these materials recognized that they were in possession of valuable insecticides and that any disaster occurring in the early stages of its introduction might have serious repercussions. All the field workers were observing simple but practical precautions such as the wearing of waterproof gloves, coats, and hats.

The greatest danger lies in the handling of the concentrated solutions of the insecticides. This is indicated by the fact that nine of the 12 workers showing evidence of absorption were factory workers.

Nearly all the reports upon the use of these substances in the field have rightly stressed their extremely toxic nature. In so doing they have tended to throw the issues out of perspective. Garlick (1950) has rightly drawn attention to the fact that many thousands of square miles have been sprayed with parathion without any accidental poisoning. The results of the present investigation offer some information on this issue. Fifty sprayers have been examined during the height of the spraying season. Between them they had sprayed hundreds of acres of fruit trees and thousands of trees. Only three of them exhibited even the slightest indication of absorption. Thirty factory workers or laboratory workers were examined. Only the use of the most stringent criterion of departures of cholinesterase levels from normality permitted the recognition of any abnormality in nine of them. Ten workers who had been engaged continuously in the manufacture of parathion for two years had normal levels of blood cholinesterase.

These facts demonstrate quite clearly that the organophosphorus insecticides may be manufactured and applied without risk provided manufacturer, consumer, and their employees co-operate by the rigid adherence to every form of safety device and procedure which has been developed for that end.

The observations here reported provide no grounds for complacency, and those who use or are responsible for encouraging the use of these materials should remember that freedom from accidents in this country during the past year has been the result of the heed given to early warnings rather than to the innocuous nature of the materials handled.

Summary

The cholinesterase levels of 80 men and women exposed to organo-phosphorus insecticides in the field or factory have been determined.

Three criteria of departure from normal variation of enzyme levels have been described. On the basis of these standards abnormal variations which are probably attributable to insecticide absorption have been recognized in 12 individuals.

The departures from normality were very slight. No serious case of poisoning was observed.

These observations emphasize the value of the test, and their significance in relation to the incidence of insecticide poisoning in field and factory workers is discussed.

We wish to acknowledge the generous help and co-operation which we received from those firms and workers, both agricultural and factory, who made this research possible. We are also very appreciative of the careful technical assistance we received from Miss A. M. Eyres. Acknowledgment is also made to the Chief Scientist, Ministry of Supply, for permission to publish this paper. Crown copyright reserved. Reproduced with permission of the Controller of H.M. Stationery Office.

REFERENCES

Abrams, H. K., Hamblin, D. O., and Marchand, John F. (1950). *J. Amer. med. Ass.*, **144**, 107.
Bidstrup, P. L. (1950). *British Medical Journal*, **2**, 548.
Callaway, S., Davies, D. R., and Rutland, J. P. (1951). Ibid., **2**, 812.
Davies, D. R., Fellowes, P. K., and Rutland, J. P. (1951). Unpublished results.
Garlick, W. L. (1950). *Industr. Hyg. Newslett.*, **10**, No. 9, 11.
Goldblatt, M. W. (1950). *Pharm. J.*, **164**, 229.
Grob, D., Garlick, W. L., and Harvey, A. M. (1950). *Bull. Johns Hopk. Hosp.*, **87**, 106.
—— Lilienthal, J. L., jun., Harvey, A. M., and Jones, B. F. (1947). Ibid., **81**, 217.
McCance, R. A. (1950). *Proc. roy. Soc. Med.*, **43**, 272.
Michel, H. O. (1949). *J. Lab. clin. Med.*, **34**, 1564.
Milles, H. L., and Salt, H. B. (1950). *British Medical Journal*, **2**, 444.
Report to Pesticides Committee (1950). *J. Amer. med. Ass.*, **144**, 104.

FAILURE OF ORAL D.D.T. TO INDUCE TOXIC CHANGES IN RATS

BY

G. R. CAMERON, M.B., D.Sc., F.R.C.P., F.R.S.

(From the Department of Morbid Anatomy, University College Hospital Medical School, London)

AND

KWOK-KEW CHENG, M.B., Ph.D.

(From the Medical Research Council Unit for Research in Toxicology, Serum Research Institute, Carshalton, Surrey)

Dichloro-diphenyl-trichloroethane (D.D.T.) remains one of the most widely used of the synthetic insecticides. Appreciable quantities may be found on food, and one report shows that fat taken from ordinary citizens not considered to have been unduly exposed to D.D.T. may contain up to 30 p.p.m. (parts per million) of the insecticide (Laug, Kunze, and Prickett, 1951). At the present time nothing is known about the action of D.D.T. beyond the fact that it interferes in some way with the normal function of the nervous system. A detailed search failed to reveal any evidence of interference with a number of enzyme systems (Judah, 1949). For this reason special importance must still be attached to histological evidence of tissue damage or change occurring in animals exposed to D.D.T.

The pathological changes occurring in animals dying of acute poisoning by D.D.T. have been described, and the most striking lesion is a severe liver necrosis (Cameron and Burgess, 1945). Despite this obvious damage to the liver tissue animals in chronic poisoning die from causes associated with injury to the central nervous system and do not show the characteristic signs of acute liver injury. Fitzhugh and Nelson (1947) claimed that they could see characteristic liver lesions in rats that had received a diet containing 100–800 p.p.m. of D.D.T. for a period of two years. The changes they found were hypertrophy of the centrolobular hepatic cells with increased oxyphilia, increased basophilia, and margination of cytoplasmic granules and a tendency to hyalinization of the remainder of the cytoplasm. Only those animals receiving 400 p.p.m. or more of D.D.T. showed any clinical evidence of poisoning.

Laug, Nelson, Fitzhugh, and Kunze (1950) fed rats for 15–27 weeks on diets containing 1 to 50 p.p.m. D.D.T. and claimed that similiar lesions developed in the liver cells of rats receiving as little as 5 p.p.m. D.D.T. These changes were much less prominent in the livers of other rodents and were never found in dogs, cats, monkeys, or the larger experimental animals. The conclusion they drew that as little as 5 p.p.m. of D.D.T. in the diet can produce recognizable changes in the structure of the hepatic cells of the rat has obvious and serious implications bearing on the question of what should be the maximum permitted limit of D.D.T. in foodstuff for human or animal consumption. The implication that a concentration of D.D.T. might be harmful has been accepted in America (Dunbar, 1949).

In 1947 a series of long-term feeding experiments on rats, fowls, sheep, pigs, and cattle were started by the Agricultural Research Council.* A large number of rats

*The Toxicity Subcommittee of the Research and Development Co-ordinating Committee on Insecticides initiated and supervised this work.

were used and they received different doses of D.D.T. Apart from those animals dying from intercurrent disease, with or without signs of D.D.T. poisoning, some of each group were killed at different times. This report outlines our observations on histological material prepared from these animals. Although the method of administration differed from that used by Laug *et al.* (1950), the dose levels were comparable and the experimental animals and the period of exposure to D.D.T. were the same. As our findings are quite different from those of the American workers we feel that they should be published because of the interest that has been aroused by the American claims.

Methods

Male and female albino rats were used when they were six weeks old, and each animal received a single dose of D.D.T. dissolved in oil six days a week. The basic dose was calculated in the following way:

Actual LD50 for rat (single dose)	300 mg./kg.
Calculated LD50 for man (70 kg.)	21 g.
Recommended dosage for treated grain	0.005%
Daily consumption of D.D.T. by a man eating 500 g. of bread a day	0.025 g.
Fraction of LD50 consumed	1/840
Basic rate of dosage for rat	1/840×300 (LD50) =0.36 mg./kg.

Groups of rats were given the basic dose, and 10 times and 100 times the basic dose. If a rat of average weight (250 g.) is assumed to consume 20 g. of food a day, the following rough equivalent for these doses in terms of parts per million D.D.T. in the diet can be calculated:

Basic dose	= 0.36 mg./kg. ≡	3.5 p.p.m.
10× „ „	= 3.6 mg./kg. ≡	35.0 „
100× „ „	=36.0 mg./kg. ≡	350.0 „

The dose of D.D.T. dissolved in arachis oil was placed on the back of the tongue of the rat and was immediately swallowed. The control animals received arachis oil only. Rats from each group were deliberately killed 33, 43, and 60 weeks after the start of the experiment. At one stage of the experiment an epidemic of pasteurellosis swept through the animal house and there were a number of incidental deaths not attributable to D.D.T. poisoning. Other animals were killed at different times during the experiment either because they had severe symptoms of poisoning by D.D.T. or had otitis media or abscesses round the jaws. The group of rats killed 43 weeks after starting D.D.T. were from a second experiment in which there were no incidental deaths.

Histological material was obtained from 123 experimental and 30 control rats. Small pieces of tissue were taken from the liver, spleen, kidney, heart, adrenals, bone marrow, and, in selected cases, from the lung and brain. They were fixed at once in 10% formol saline and 10% formol alcohol, but some were fixed in Helly's fluid. Paraffin sections were prepared in the usual way and stained with Ehrlich's acid haematoxylin and eosin and with van Gieson. In most cases fat staining with Sudan III was also done.

The animals from which the material was obtained were from the groups fed at different levels of D.D.T. for different periods. The numbers from each are given in the Table.

Source of Histological Material from Rats Fed D.D.T. for Long Periods

1. *Number of healthy rats deliberately killed*

Daily Dose of D.D.T.	Period of Treatment (Weeks)			Total No. of Animals
	33	43	63	
0·36 mg./kg. ..	6	6	6	18
3·6 „ ..	6	8	6	20
36·0 „ ..	6	5	6	17
Nil „	6	14	6	26

2. *Rats dying from intercurrent disease*

Total number that had received D.D.T.	68
Number killed or dying with signs of poisoning	11
Controls	4
Total ..	72

Results

The organs of the rats that had received D.D.T. showed no consistent changes. Special attention was paid to the liver of those rats that were deliberately killed at different times after starting the administration of D.D.T. There was slight focal necrosis in 3, portal infiltration in 8, a tapeworm cyst in 1, and some regenerative change in 1. Thus changes were seen in 13 out of 55 rats. Among the 26 control rats focal necrosis was observed in 7 cases and portal infiltration in 11.

A special search was made for signs of regeneration in the liver—namely, areas showing loss of normal lobular pattern, irregular size of liver cells, and presence of double nuclei. If these had been found we might have concluded with reason that D.D.T. had produced damage at some stage, with subsequent recovery. This, however, was not the case. Among the 68 rats dying from intercurrent infections or killed because they were ill, the livers of two female rats showed changes that could be associated with D.D.T. poisoning. Both rats had received 10 times the basic dose (3.6 mg./kg. daily, or approximately 35 p.p.m.) for 45 and 60 weeks. Both presented centrolobular necrosis, and this was attributed to D.D.T. because careful search failed to disclose the additional changes due to infection. The appearance did not suggest prolonged damage but rather an acute disturbance starting shortly before death. With these exceptions no characteristic lesions could be found even in the rats dying with the signs of severe D.D.T. poisoning. Lipoid pneumonia and pulmonary oedema caused the death of 12 rats in this group; these conditions were no doubt the result of aspiration of the oily solution of D.D.T.

A special search was made for the hepatic lesions which had been described by Fitzhugh and Nelson (1947) and Laug *et al.* (1950) as characteristic of chronic D.D.T. poisoning. Basophilic cytoplasmic granules are a common feature in rat liver cells, and their margination is sometimes observed in both experimental and control groups. No significant difference in the extent of these changes could be made out between the two groups. No convincing evidence of hypertrophy of liver cells was found in rats that had received D.D.T. Increased cytoplasmic oxyphilia and hyalinization of the cytoplasm were not observed in any animal.

Discussion

Rats receiving 0.36, 3.6, and 36 mg. of D.D.T. per kg. for six days a week have been carefully examined after 33, 43, and 60 weeks of treatment, but no histological evidence of any changes in the liver cells has been

obtained. Such changes as were seen—focal necrosis or portal infiltration—were found to an equal extent in the control animals of the same age which had received arachis oil only. Among the 68 rats dying during the course of the experiments liver necrosis characteristic of acute poisoning with D.D.T. was seen in two. This suggested that there had been an acute lowering of the animal's tolerance to D.D.T. owing to intercurrent infection. No rat showed any histological evidence that could be called characteristic of chronic D.D.T. poisoning. The findings of Fitzhugh and Nelson (1947) and Laug *et al.* (1950) have not been confirmed. Sections of normal rat liver were compared after fixation in 10% formalin, 10% formol saline, and Helly's fluid for various periods and staining with haematoxylin and eosin. Basophilic cytoplasmic granules are often observed in the normal rat liver cells. Margination of basophilic cytoplasmic granules are common fixation artifacts. They are seen especially in formalin-fixed tissues and are more marked if the tissue is deliberately badly fixed. Formalin is not a suitable fixative for cytological study. The photomicrographs that illustrate the paper of Laug *et al.* (1950) suggest badly fixed tissues.

Summary

Rats given 0.36, 3.6, and 36 mg. D.D.T. per kg. daily for up to 60 weeks showed no lesions that were characteristic of chronic poisoning with D.D.T. The incidence of naturally occurring pathological lesions was equally distributed among the rats receiving D.D.T. and among the control rats receiving arachis oil alone. No significant structural disturbance has been found in the kidneys and heart.

We gratefully acknowledge much assistance from Brigadier A. Sachs, Director of Pathology for the Army, and Mr. Solomon, of the Agricultural Research Council's staff.

REFERENCES

Cameron, G. R., and Burgess, F. (1945). *British Medical Journal*, 1, 865.
Dunbar, P. B. (1949). *Food, Drug, Cosmetic Law Quart.*, p. 233.
Fitzhugh, O. G., and Nelson, A. A. (1947). *J. Pharmacol.*, 89, 18.
Judah, J. D. (1949). *Brit. J. Pharmacol.*, 4, 120.
Laug, E. P., Kunze, F. M., and Prickett, C. S. (1951). *Arch. industr. Hyg.*, 3, 245.
—— Nelson, A. A., Fitzhugh, O. G., and Kunze, F. M. (1950). *J. Pharmacol.*, 98, 268.

Replies to a questionary on student health sent out to universities in 53 countries had been received by the International Association of University Professors and Lecturers from 23 countries at the time of the Basle conference in 1949. The Association had decided at a previous conference that the universities should undertake a fuller responsibility for the health of their students, and recommended that arrangements should be made to examine students both before and regularly after entry. The replies made it quite clear that importance is generally attached to chest examinations; on the other hand, most universities are against any exacting psychological examination of the ordinary student's mental health, and an indirect approach is favoured. Prague uses intelligence tests as part of the entrance examination. Out of 91 universities having student health schemes, only about 40 provide physical education for those who do not take part in athletics. Closer supervision of lodgings and hostels is advocated, and the importance of adequate nourishment is stressed. Instruction in personal and social hygiene is also advised, and the establishment of suitable amenities for looking after students who are ill; some universities have sick wards in their residence, others utilize the State health service. Full details of the conditions existing in various universities are published in *Communication 16, Report on Student Health Services* (I.A.U.P.L., London, W.C.2, price 1s.).

PRELIMINARY FIELD TRIALS ON A NEW SCHIZONTICIDE

BY

H. M. ARCHIBALD, M.B.E., M.B., Ch.B.
Malaria Service, Medical Department, Nigeria

"B.W. 50–63" is one of a series of 2,4-diamino-pyrimidines, being 2,4-diamino 5-*p*-chlorophenyl 6-ethyl pyrimidine. Certain similarities which this compound and proguanil showed in their antagonistic action on pteroylglutamic acid suggested that it might have antimalarial activity (Falco *et al.*, 1949), and this was shown to be the case (Falco *et al.*, 1951).

At the time these field trials started, laboratory experiments had shown that this drug was a successful schizonticide against *Plasmodium gallinaceum* in chicks, *P. cynomolgi* in monkeys, and *P. berghei* in mice. Toxicity tests on chicks had shown that, weight for weight, the drug had a toxicity similar to that of proguanil, but as its effective dose promised to be small its active dose would be safer in practice. B.W. 50–63 was 60 times as active as proguanil against *P. gallinaceum* and 200 times as active against *P. berghei*. The drug was also active against the blood-forms of *P. cynomolgi* in monkeys, but had no pronounced action upon the exoerythrocytic stages (Falco *et al.*, 1951). It was decided to test this drug in accordance with the method introduced by Bruce-Chwatt (1951) and recommended at the World Health Organization's Conference on Malaria in Africa (1951). A number of African children naturally infected with malaria, of age group 5–10 years inclusive, were used, drawn from schools in the vicinity of Lagos.

Observations of splenic enlargement were made on standing children by a seated observer, and the results were classified in accordance with Hackett's classification (Hackett, 1944). Parasite rates and densities were calculated from observations made on thick films, "negatives" being determined only after the examination of 200 thick-film fields. Parasite density counts were made by determining the parasite/leucocyte ratio from the thick film and calculating from that the number of parasites per c.mm. The rates recorded are those generally accepted. The indices recorded are:

1. *The average enlarged spleen:* an index of the size of splenic enlargements in a group. It is obtained by multiplying the number of individuals in each spleen size group (Hackett's classification) by the group number, and dividing the sum of these products by the total number of those examined who are found to have enlarged spleens.

2. *The parasite density index:* an index of the density of parasitaemia in a group. It is obtained by multiplying the number of individuals in each parasite density group (Bruce-Chwatt, 1951) by the arbitrary group number, and dividing the sum of those products by the total number of individuals examined.

A preliminary test was carried out on a selected group of 12 indigenous schoolchildren, from a suburb of Lagos, whose bloods showed the presence of numerous *P. falciparum* trophozoites on D−1 and D day. On D day a single tablet of 25 mg. of the drug was taken by each child by mouth in the presence of the examiner. This preliminary test was carried out against control groups of untreated children and of children treated with 300 mg. proguanil in a single dose, orally,

on D day. The results of this preliminary test are given in Table I. They show: (i) that the drug was able to clear the blood of *P. falciparum* trophozoites by D+4 day; (ii) that neither *P. falciparum* gametocytes nor *P. malariae* were eliminated by B.W. 50–63 by D+7 day. A continuation of the trials appeared justified.

The next step was to discover if B.W.50–63 in this dosage cleared the blood any earlier than D+4 day, as a guide to the possible value of the drug as a "curative" as compared with its action as a "suppressive." Observations to this end were made on further groups of schoolchildren, selected as in the first test, and these observations were again made in comparison with controls as in the earlier investigation. An additional control group treated with 300 mg. mepacrine, given in a single oral dose on D day, was also included in this test, in view of the accepted place of mepacrine as a quick-acting schizonticide. Data were collected on D, D+1, D+2, D+3, and D+4 days. The results are shown in Table II. They confirmed the findings of the first test, but suggest that B.W. 50–63 will clear the blood of *P. falciparum* trophozoites by D+3. The mepacrine control group, however, showed that mepacrine had an earlier effect.

In view of the results of these trials it was decided to investigate the persistence of B.W. 50–63 and its action when given in much lower doses than those tested before. Groups of schoolchildren, selected as already described, were tested against single oral doses on D day of (i) 10 mg. B.W. 50–63 and (ii) 5 mg. B.W. 50–63.

Observations were made on D, D+4, D+7, D+14, D+30, and D+ (60±15). The results are shown in Table III. They demonstrate that 5 mg. of the drug was quite as effective as many of the larger doses given

TABLE I.—*Preliminary Trials of B.W. 50–63*

	Untreated Controls Spleen Rate on D Day 7/12 = 58% Average Enlarged Spleen on D Day 15/7 = 2·1					Group Treated with 300 mg. Proguanil Spleen Rate on D Day 5/13 = 38% Average Enlarged Spleen on D Day 12/5 = 2·4					Group Treated with 25 mg. B.W. 50–63 Spleen Rate on D Day 11/12 = 92% Average Enlarged Spleen on D Day 25/11 = 2·3				
	−D	D	D+1	D+4	D+7	−D	D	D+1	D+4	D+7	−D	D	D+1	D+4	D+7
No. examined	12	11	12	12	10	13	13	12	13	13	12	12	12	12	12
No. absent	—	1	0	0	2	—	0	1	0	0	0	0	0	0	0
Crude parasite rate	12/12	10/11	9/12	11/12	9/10	13/13	12/13	10/12	2/13	3/13	12/12	12/12	12/12	6/12	5/12
	100·0	91·0	75·0	91·6	90·0	100·0	92·0	83·5	15·4	23·0	100·0	100·0	100·0	50·0	41·6
P. falciparum trophozoite rate	12/12	10/11	9/12	10/12	9/10	13/13	12/13	9/12	0/13	0/13	12/12	12/12	12/12	0/12	0/12
	100·0	91·0	75·0	91·6	90·0	100·0	92·0	75·0	0	0	100·0	100·0	100·0	0	0
P. falciparum gametocyte rate	1/12	2/11	2/12	4/12	3/10	2/13	2/13	4/12	2/13	3/13	1/12	1/12	5/12	6/12	5/12
	8·3	18·1	16·7	33·3	30·0	15·4	15·4	33·0	15·4	23·0	8·3	8·3	41·6	50·0	41·6
P. malariae rate	1/12	1/11	0/12	1/12	1/10	2/13	1/13	2/12	1/13	0/13	0/12	1/12	1/12	1/12	1/12
	8·3	9·1	0	8·3	10·0	15·4	7·7	16·7	7·7	0	0	8·3	8·3	8·3	8·3
P.D.I.	47/12	35/11	18/12	24/12	28/10	47/13	49/13	27/12	3/13	3/13	55/12	38/12	35/12	8/12	6/12
	3·9	3·2	1·5	2·0	2·8	3·6	3·8	2·3	0·2	0·2	4·6	3·2	2·9	0·75	0·5

TABLE II.—*Tests of the Possible Value of B.W. 50–63 as a "Curative"*

	Untreated Controls Spleen Rate on D Day 2/5 = 40% A.E.S. on D Day 4/2 = 2					Group Treated with 300 mg. Proguanil Spleen Rate on D Day 14/16 = 87·5% A.E.S. on D Day 30/14 = 2·1					Group Treated with 300 mg. Mepacrine Spleen Rate on D Day 13/14 = 93 A.E.S. on D Day 36/13 = 2·6					Group Treated with 25 mg. B.W. 50–63 Spleen Rate on D Day 9/10 = 90% A.E.S. on D Day 18/9 = 2				
	D	D+1	D+2	D+3	D+4	D	D+1	D+2	D+3	D+4	D	D+1	D+2	D+3	D+4	D	D+1	D+2	D+3	D+4
No. examined	5	4	4	4	4	16	14	16	14	16	14	13	12	13	12	10	10	9	10	10
No. absent	0	1	1	1	1	0	2	0	2	0	—	1	2	1	2	0	0	1	0	0
Crude parasite rate	5/5	4/4	4/4	3/4	4/4	16/16	13/14	10/16	7/14	4/16	14/14	9/13	1/12	5/13	1/12	10/10	9/10	4/9	5/10	4/10
	100·0	100·0	100·0	75·0	100·0	100·0	93·0	62·5	50·0	25·0	100·0	69·0	8·3	38·5	8·3	100·0	90·0	44·4	50·0	40·0
P. falciparum trophozoite rate	5/5	4/4	4/4	2/4	3/4	15/16	12/14	1/16	1/14	0/16	12/14	5/13	0/12	1/13	0/12	9/10	8/10	1/9	0/10	0/10
	100·0	100·0	100·0	50·0	75·0	94·0	86·0	6·25	7·1	0	85·75	38·5	0	7·7	0	90·0	80·0	11·1	0	0
P. falciparum gametocyte rate	1/5	0/4	2/4	2/4	1/4	2/16	2/14	5/16	3/14	3/16	1/14	4/13	1/12	5/13	1/12	2/10	4/10	2/9	4/10	3/10
	20·0	0	50·0	50·0	25·0	12·5	14·3	31·3	21·4	18·75	7·1	30·8	8·3	38·5	8·3	20·0	40·0	22·2	40·0	30·0
P. malariae rate	1/5	2/4	1/4	0/4	0/4	6/16	6/14	7/16	4/14	1/16	4/14	1/13	0/12	1/13	0/12	1/10	4/10	2/9	1/10	1/10
	20·0	50·0	25·0	0	0	37·5	43·0	43·75	28·6	6·25	28·6	7·7	0	7·7	0	10·0	40·0	22·2	10·0	10·0
P. vivax rate	—	—	—	—	—	—	—	—	—	—	1/14	1/13	0/12	1/13	0/12	1/10	1/10	0/9	1/10	1/10
	—	—	—	—	—	—	—	—	—	—	7·1	7·7	0	7·7	0	10·0	10·0	0	10·0	10·0
P.D.I.	16/5	11/4	13/4	5/4	11/4	55/16	43/14	21/16	8/14	4/16	60/14	17/13	1/12	7/13	1/12	32/10	25/10	6/9	6/10	4/10
	3·2	2·8	3·25	1·25	2·8	3·4	3·1	1·3	0·57	0·25	4·3	1·3	0·1	0·5	0·1	3·2	2·5	0·7	0·6	0·4

TABLE III.—*Tests of the Persistence of the Action of B.W. 50–63*

	Group Treated with 10 mg. B.W. 50–63						Group Treated with 5 mg. B.W. 50–63					
	D	D+4	D+7	D+14	D+30	D+60	D	D+4	D+7	D+14	D+30	D+60
No. examined	34	29	30	30	11*	24	48	28*	44	40	27*	31
No. absent	0	5	4	4	6	10	0	3	4	8	4	17
Spleen rate	24/32			13/28	6/11	4/14	34/45			14/40	10/27	13/30
	75·0			46·5	54·5	28·6	75·6			35·0	37·0	43·0
A.E.S.	48/24			25/13	10/6	7/4	69/34			22/14	14/10	23/13
	2·0			1·9	1·7	1·8	2·0			1·6	1·4	1·8
Crude parasite rate	34/34	12/29	3/30	2/30	1/11	11/24	48/48	5/28	11/44	1/40	1/27	11/31
	100·0	35·5	10·0	6·6	9·1	46·0	100·0	17·9	25·0	2·5	3·7	35·0
P. falciparum trophozoite rate	30/34	2/29	1/30	1/30	1/11	10/24	45/48	0/28	1/44	0/40	0/27	11/31
	88·0	6·9	3·3	3·3	9·1	41·6	93·8	0	2·3	0	0	35·0
P. falciparum gametocyte rate	10/34	7/29	1/30	2/30	0/11	3/24	6/48	4/28	11/44	1/40	1/27	0/31
	29·4	24·2	3·3	6·6	0	12·5	12·5	14·3	25·0	2·5	3·7	0
P. malariae rate	8/34	6/29	2/30	0/30	0/11	0/24	8/48	3/28	1/44	0/40	0/27	1/31
	23·6	20·7	6·7	0	0	0	16·7	10·7	2·3	0	0	3·2
P.D.I.	125/34	17/29	3/30	5/30	1/11	42/24	183/48	7/28	11/44	1/40	1/27	33/31
	3·7	0·6	0·1	0·2	0·09	1·75	3·8	0·25	0·25	0·03	0·04	1·1

* Only one school available.

during these trials; that this dosage was effective in clearing most trophozoites of *P. falciparum* from the blood of the observed group by D+4 day, but that occasional parasites persisted; that *P. malariae* parasites, although persisting in the blood for more than seven days after treatment, do eventually disappear; that the effect of a single dose of B.W. 50–63, as assessed by parasite density indices, spleen rates, and average enlarged spleens, appears to persist for one month but to be lost during the next month.

During the preliminary trials no unexplained absence occurred among the 22 children treated with 25 mg. B.W. 50–63, and no complaint of headache, nausea, or vomiting was made by any of these children.

My thanks are due to Dr. S. L. A. Manuwa, O.B.E., Director of Medical Services, Nigeria, and to Dr. L. J. Bruce-Chwatt, Senior Malariologist i/c Malaria Service, Medical Department, Nigeria, for permission to publish this paper. I am also grateful to Brigadier J. S. K. Boyd, F.R.S., and Dr. L. G. Goodwin for providing supplies of B.W.50-63, and for advance information on laboratory investigations.

REFERENCES

Bruce-Chwatt, L. J. (1951). *Trans. roy. Soc. trop. Med. Hyg.*, **44**, 563.
Falco, E. A., Hitchings, G. H., Russell, P. B., and Vander-Werff, H. (1949). *Nature, Lond.*, **164**, 107.
—— Goodwin, L. G., Hitchings, G. H., Rollo, I. M., and Russell, P. B. (1951). *Brit. J. Pharmacol.*, **6**, 187.
Hackett, L. W. (1944). *J. nat. Malar. Soc.*, **3**, 121.
W.H.O. Tech. Report Series No. 38 (1951). Malaria Conference in Equatorial Africa. Geneva.

VALUE OF GASTRIC BIOPSY IN THE STUDY OF CHRONIC GASTRITIS AND PERNICIOUS ANAEMIA*

BY

IAN J. WOOD, M.D., F.R.C.P.

Assistant Director, Walter and Eliza Hall Institute of Medical Research, Melbourne

I deeply appreciate the honour of being invited to deliver the Litchfield Lecture of 1951. It is the ambition of every Australian to visit Oxford, and I am most grateful for this additional privilege. I thought it would be of the greatest interest to you if I discussed the investigations we have been carrying out in Australia during the past three years on the gastric mucosa and its relationship to disease.

In 1946 Sir Macfarlane Burnet established a clinical research unit at the Walter and Eliza Hall Institute of Medical Research and the Royal Melbourne Hospital to work in the wards of the hospital and in the adjoining laboratories of the institute, and I have the privilege of being a member of this unit. We chose the alimentary canal for our studies, employing clinical observation, serial biochemical tests, *x*-ray examination, gastroscopy, and liver biopsy. We soon began to encounter a group of patients, mostly women between the ages of 35 and 60, who complained of long-standing relapsing flatulent dyspepsia, and examination of whom revealed diffuse epigastric tenderness, negative findings to a barium meal, persistent histamine-fast achlorhydria or hypochlorhydria, and rather inconclusive findings on gastroscopy. We were investigating one of these patients by test meal one day when a fragment of tissue was sucked out through the Ryle's tube. On section, this proved to be gastric epithelium. With considerable trepidation we then set out to obtain fragments of gastric mucosa in order to correlate their histological structure with the symptoms, signs, and biochemical tests, just as we had been doing with some success with liver fragments obtained by needle biopsy.

*An abstract of the Litchfield Lecture given at Oxford on June 6.

The Biopsy Procedure

In collaboration with A. Hughes, of our institute, a flexible gastric biopsy tube has been developed during the past three years (Wood, Doig, Motteram, and Hughes, 1949; Wood, Doig, Motteram, Weiden, and Moore, 1949). It consists of a length of Bowden wire covered with plastic tubing to render it airtight. At the distal end is a metal cylinder housing a cylindrical knife, which can be moved up and down past a lateral hole by means of a wire which passes through the whole length of the instrument. The tube can be passed readily into the empty stomach. Negative pressure is exerted at the upper end, and this sucks in a knuckle of gastric mucosa through the lateral hole at the lower end. This knuckle of gastric mucosa is then cut off by pulling up the knife. The procedure is easily performed and causes little inconvenience to the patient. A fragment of mucosa 2 mm. in diameter and extending down to the muscularis mucosae is obtained. In the last 100 attempts at biopsy my colleague, R. K. Doig, has obtained fragments of gastric mucosa in 92.

The fragment is most frequently removed from the greater curvature of the body of the stomach. This has been confirmed by *x*-ray examination with the tube *in situ* and by gastroscopy carried out immediately after the biopsy,when the biopsy site can usually be seen. In this lecture I refer to fragments removed from the body of the stomach.

The complications following biopsy have been few. We have performed 552 biopsies on 462 patients and there has been no evidence of perforation or established ulceration. Haemorrhage in the form of haematemesis or melaena has occurred in six cases, but on no occasion has it seemed to threaten life.

In our unit Gunter has studied the lesion produced in the gastric mucosa of the cat when the same biopsy instrument is used. He found that there was rapid healing of the traumatized area. Two days after taking the fragment regeneration of the surface epithelium was seen, and it completely covered the area by the third day. By the eighth day almost complete healing had taken place, but acid- and pepsin-secreting cells were not identified.

The history of gastric biopsy is of interest. In 1894, Einhorn, of New York, collected fragments of gastric mucosa by vigorous aspiration with a stomach tube, and in 1906 Chevalier Jackson, of Philadelphia, skilfully carried out biopsy through his rigid oesophagoscope. Little attention was paid to his findings. It fell to the lot of two Americans—Kenamore, in 1946, and Benedict, in 1948—to draw attention to the value of the procedure, using an operating gastroscope.

Types of Lesion Investigated

I propose to discuss several patients seen in our unit who are representative of the three groups of diffuse gastric lesions which we have sorted out with the help of our pathologist, R. Motteram. I shall not discuss gastric ulcer or carcinoma, for here the mucosal changes

are not evenly spread; there is a zonal gastritis extending out from the lesion, giving variable findings. In duodenal ulcer, gastric biopsy of the body of the stomach usually shows a normal mucosa. It has been normal in 21 out of 29 cases. Of course, with duodenal ulcer there may be gastritis in the antrum.

We have found three main types of lesion in the gastric mucosa which, from a histological point of view, we had classified as superficial gastritis, atrophic gastritis, and gastric atrophy. We consider that superficial gastritis may resolve or may progress to atrophic gastritis, whereas once the stage of atrophic gastritis is reached there appears to be little or no tendency to resolution. The third group, gastric atrophy, shows minimal evidence of inflammatory reaction, there is gross atrophy of the acid- and pepsin-secreting cells, and the lesion is usually associated with pernicious anaemia and/or subacute combined degeneration of the cord.

Superficial Gastritis

Case 1.—An intelligent housewife aged 37 had suffered from intermittent flatulent dyspepsia for the past six years. Her symptoms began after taking large doses of aspirin for an attack of influenza. She suffered from intermittent attacks of burning epigastric pain and flatulence, coming on soon after taking food and relieved by alkali. She was a sensible but nervy woman and had considerable domestic worry. Her appetite was poor and her diet had been somewhat deficient, as she had many fads. Her symptoms were aggravated by periods of worry and subsided when she was on holiday. Examination showed slight atrophy of the tongue, diffuse epigastric tenderness, more pronounced during the exacerbations of symptoms, negative barium-meal test, and negative gastroscopy. There was no occult blood in the stools. We studied her over a period of three years with serial biopsies and test meals; the test meals always showed hypochlorhydria or achlorhydria and the biopsies superficial gastritis. During one acute attack she was admitted to the ward and treated with penicillin, administered by mouth, apparently with some benefit.

Case 2.—A housewife aged 43 suffered from flatulent dyspepsia for three months and then from biliary colic and jaundice. Operation revealed stones in the common duct and gall-bladder. These were removed, together with the gall-bladder. She remained well during the next three years except for slight flatulent dyspepsia, and on one occasion a gastro-duodenal haemorrhage with a fall in haemoglobin and with occult blood in the stools. Repeated test meals before and after operation showed histamine-fast achlorhydria. Gastric biopsy revealed superficial gastritis with diffuse superficial haemorrhage.

This finding of haemorrhage in the biopsy fragment was probably due to trauma at the time of taking the biopsy, but we have found it more often in the mucosa of patients suffering from gastritis than in the normal mucosa. It would appear that gastritis may lead to recurrent gastric bleeding—usually of minor degree, but sometimes more formidable. We believe that chronic gastritis may sometimes contribute to the anaemia seen in "Witts's anaemia." On rare occasions the haemorrhage may reach the severity encountered in bleeding peptic ulcer. It may then present a problem to the surgeon as well as to the physician.

Superficial gastritis appears to be associated with chronic flatulent dyspepsia which waxes and wanes, often influenced by worry, malnutrition, or alcoholism. Slow but persistent haemorrhage may occur. Superficial gastritis may resolve, especially if the causal factor, such as acute alcoholism, is removed. It is associated with hypochlorhydria or achlorhydria. If it resolves there is improvement in the patient's symptoms, the level of the free acid, and the biopsy picture. It may progress to atrophic gastritis, with persistent achlorhydria and perhaps more pronounced symptoms.

Atrophic Gastritis

Atrophic gastritis would appear to be an advanced stage of superficial gastritis; here there is atrophy of the acid- and pepsin-secreting cells in addition to the inflammatory reaction.

Case 3.—A woman aged 62 suffered from flatulent dyspepsia for six years. Her diet was deficient. She was not an alcoholic. She had pain in the epigastrium immediately after taking food, which was often relieved by alkaline powder. Her appetite was poor and there was no vomiting. Her tongue was atrophic, cheilosis occurred at the corners of the mouth, and there was epigastric tenderness. Repeated test meals over two years showed persistent achlorhydria. Barium meal tests were negative and gastric biopsy showed severe atrophic gastritis. With an explanation of her condition, encouragement to take a good diet, and rest in bed during the acute exacerbations, she has maintained moderately good health. Serial biopsies over a two-year period showed no tendency to regeneration of the specific acid- and pepsin-secreting cells, and the inflammatory changes varied only slightly.

Case 4.—This patient, aged 64, had been a healthy young woman when she went to India in the Australian Nursing Service during the 1914–18 war. On the Northern Frontier she developed malaria and dysentery, and the food was of very poor quality. She returned to Australia two years later, wasted and weak, a shadow of her former self. She has never completely recovered. She has remained thin, with flatulent dyspepsia, hypochromic anaemia relieved by iron, koilonychia, constant histamine-fast achlorhydria, and often occult blood in the stools. Gastric biopsy showed atrophic gastritis. When given iron, encouragement to take a full diet, and the reassurance that she did not have cancer, she remained in moderately good health during the next three years. In fact, she has given great help to our unit by volunteering to be the subject of some of our studies. She has provided most valuable evidence that the mucosal lesion in chronic atrophic gastritis undergoes little change with the passage of years.

It is our belief that atrophic gastritis may cause recurrent flatulent dyspepsia, atrophy of the tongue, constant hypochlorhydria or more often achlorhydria, and be negative to a barium meal test. There may be hypochromic anaemia, due in part to blood loss from the mucosa, malnutrition, and impaired intestinal absorption of iron. There appears to be little or no evidence that pernicious anaemia or subacute combined degeneration of the cord occurs in this group. Neither is there any tendency to complete recovery except, perhaps, in the case of the irradiated stomach (see below).

Gastric Atrophy

Our studies of the gastric mucosa naturally led us to consider the histological picture in cases of pernicious anaemia and subacute combined degeneration of the cord (Doig, Motteram, Robertson, and Wood, 1950). We have found that, in pernicious anaemia, (1) there is severe atrophy of the gastric mucosa with a tendency to intestinal metaplasia; (2) there is complete or almost complete absence of the inflammatory changes seen in superficial gastritis and atrophic gastritis; (3) the mucosa shows no tendency to regenerate when given standard liver therapy over a period of years—one case was examined by Doig and Motteram after thirteen years of adequate liver therapy; and (4) the mucosa does not regenerate when given liberal weekly injections of

vitamin B_{12}. We have termed this lesion of pernicious anaemia and subacute combined degeneration of the cord "gastric atrophy," in contradistinction to superficial gastritis and atrophic gastritis.

Case 5.—A chocolate manufacturer aged 47 was found to be suffering from typical pernicious anaemia with haemoglobin of 7.5 g. which responded to intramuscular "campolon." Stomach biopsy was performed before treatment and after three, six, and fifteen months' treatment. He was then given a four-months course of treatment with 80 μg. of vitamin B_{12} weekly. The biopsy was repeated. The gastric mucosa was found by Funder to have remained unchanged. Serial test-meal examinations showed histamine-fast achlorhydria.

What is the correlation between the histological findings and the clinical picture? Of 41 patients showing "gastric atrophy" in the gastric mucosa, 39 had pernicious anaemia and/or subacute combined degeneration of the cord. Thus we have two patients who perhaps may be expected to develop pernicious anaemia and/or subacute combined degeneration of the cord during the next few years. On the other hand, of 66 cases with "atrophic gastritis" only five had pernicious anaemia and/or subacute combined degeneration of the cord.

We have found three cases of probable subacute combined degeneration of the cord with a normal peripheral blood picture and bone marrow and with changes in the gastric mucosa identical with those of pernicious anaemia.

Moreover, we have found gastric biopsy to be of value in diagnosing those patients with possible subacute combined degeneration of the cord or pernicious anaemia who unfortunately have had treatment with liver before an adequate blood examination has been performed and whose nervous lesions are not entirely typical.

When does this gross atrophy of the gastric mucosa occur (Doig, Motteram, Weiden, and Wood, 1950; Doig, and Wood, 1950)? We do not know. Perhaps we have a slight clue. We did test meals on 134 apparently healthy medical students and found only one with persistent histamine-fast achlorhydria. This young man, whom we have called subject X, had suffered no dyspepsia. His mother had hypochlorhydria to gruel when aged 44, and his maternal grandmother had died of pernicious anaemia at the age of 70. Gastric biopsy showed considerable atrophy of the chief and parietal cells but with little inflammatory reaction. However, the change was not as pronounced as in pernicious anaemia. We shall watch his future with great interest.

Atrophic gastritis can be produced artificially by applying deep *x*-ray therapy to the gastric mucosa. This has been shown by Palmer, in America, and by Holman, in Tasmania, to be of benefit in some cases of duodenal ulcer with high gastric acidity. Thus, a textile worker, aged 36, with duodenal ulcer which did not respond to medical treatment had a normal gastric biopsy prior to irradiation. He was then given a three-weeks course of 2,000 r by Kaye-Scott. In our unit, Doig, Funder, and Weiden studied his progress in considerable detail over a period of 15 months and found that the inflammatory reaction and atrophy became pronounced, with the development of achlorhydria and greatly diminished pepsin secretion one month after the course of treatment (Doig, Funder, and Weiden, 1951). The mucosal changes remained thus for one month and then gradually returned to a normal appearance with rising acid and pepsin secretion. Normal findings were observed after the lapse of one year. This close correlation between the test-meal findings and the appearance of the gastric mucosa is in keeping with our general experience (Wood, Doig, Motteram, Weiden, and Moore, 1949).

Conclusion

I should like to emphasize that in our opinion diffuse lesions of the mucosa of the body of the stomach occur and may produce symptoms. Superficial gastritis with flatulent dyspepsia may heal or progress to atrophic gastritis. Atrophic gastritis causes recurrent flatulent dyspepsia and shows little or no tendency to heal. Severe gastric atrophy without inflammatory changes is associated with pernicious anaemia and/or subacute combined degeneration of the cord, and is probably not the end-stage of chronic gastritis. It may well be a slow atrophic process of different aetiology. Much has to be learned of the aetiology, course, and prevention of superficial gastritis, atrophic gastritis, and gastric atrophy. If we discovered how to prevent gastric atrophy perhaps we could prevent the onset of pernicious anaemia or the more tragic disease, subacute combined degeneration of the cord.

References

Doig, R. K., Funder, J. F., and Weiden, S. (1951). *Med. J. Aust.*, **1**, 828.
—— Motteram, R., Robertson, E. G., and Wood, I. J. (1950). *Lancet*, **2**, 836.
—— —— Weiden, S., and Wood, I. J. (1950). Ibid., **1**, 948.
—— and Wood, I. J. (1950). *Med. J. Aust.*, **2**, 565.
Wood, I. J., Doig, R. K., Motteram, R., and Hughes, A. (1949). *Lancet*, **1**, 18.
—— —— —— Weiden, S., and Moore, A. (1949). *Gastroenterology*, **12**, 949.

VITAMIN B_{12} IN MEGALOBLASTIC ANAEMIA OF PREGNANCY AND TROPICAL NUTRITIONAL MACROCYTIC ANAEMIA

BY

S. CHAUDHURI, M.B., M.R.C.P., D.C.H.

Professor of Medicine, Lady Hardinge Medical College, New Delhi

The value of vitamin B_{12} in Addisonian pernicious anaemia, subacute combined degeneration, nutritional macrocytic anaemia, and tropical macrocytic anaemia has been thoroughly acknowledged (West, 1948; Berk *et al.*, 1948, ; Ungley, 1948a; Hall and Campbell, 1948a, 1948b; Spies *et al.*, 1948a, 1948b; 1949; Patel, 1948, 1950; Das Gupta, 1950). Reports of its use in megaloblastic ("pernicious") anaemia of pregnancy, however, are contradictory. Ungley (1948b), Bethell *et al.* (1948), Day *et al.* (1949), and Das Gupta (1950) used it without any response, while Patel and Kocher (1950) reported its successful use in five cases of anaemia of pregnancy and the puerperium. Patel (1950) also reported that a higher dosage was required in tropical macrocytic anaemia and in megaloblastic anaemia of pregnancy than in pernicious anaemia. A report of 21 cases of megaloblastic anaemia in women patients admitted under my care at Lady Hardinge Hospital, New Delhi, and treated with vitamin B_{12}, is here presented.

TABLE I.—*Haematological Responses to Injection of Vitamin B_{12}*

Case No.	Daily Dosage (μg.)	Maximal Retic.	Day of Treatment	Hb (g./100 ml.)	R.B.C. (mil./c.mm.)	P.C.V. %	M.C.V. (μ³)	M.C.H. (μμg.)	M.C.H.C. (%)	Weekly R.B.C. Rise (mil./c.mm.)	Expected R.B.C. Rise (mil./c.mm.) (Della Vida and Dyke)
1 ..	5	15·1%	0	3·4	0·96	10·0	104	35	34.0	0·49	0·73
		14th day	54	12·6	4·82	40·0	83	26	31·5		
2 ..	7	17·5%	0	2·0	0·82	9·0	112·5	25	22·0	0·36	0·75
		15th day	53	10·0	3·50	31·0	88	32	32·0		
3 ..	4	20·2%	0	3·4	1·28	13·0	100	26	26·0	0·90	0·66
		13th day	25	12·3	4·50	32·0	71	27	38·7		
4 ..	4	15·0%	0	5·7	2·15	22·0	102	27	26·0	0·40	0·68
		9th day	15	8·1	2·95	—	—	—	—		
5 ..	4	3·5%	0	3·4	1·03	10·0	99	33	34·0	—	0·72
		4th day	15	4·08	1·20	12·0	100	34	24·0		
6 ..	9	15·0%	0	2·0	0·9	9·0	100	22	2·0	0·51	0·73
		19th day	35	10·0	3·5	30·0	86	28	33·0		
7 ..	5	20·8%	0	2·7	1·07	12·0	112	27	23·0	0·83	0·71
		11th day	22	8·5	3·50	24·0	70	24	35·0		
8 ..	7	11·5%	0	3·4	1·20	13·0	108	28	26·0	0·91	0·67
		7th day	12	5·0	2·60	18·5	71	19	27·0		
9 ..	4	25·0%	0	4·08	1·20	15·0	125	34	27·0	0·77	0·67
		7th day	20	10·0	3·50	30·0	86	28	33·0		
10 ..	4	22·5%	0	3·7	1·02	12·0	117	36	30·0	0·80	0·72
		9th day	30	10·5	4·30	38·0	89	24	27·0		
11 ..	10	15·1%	0	3·70	1·10	12·0	109	34	31·0	1·06	0·70
		9th day	22	10·54	4·30	32·0	74	25	33·0		
12 ..	11	21·5%	0	3·70	1·02	12·0	117	36	30·0	0·93	0·72
		5th day	20	9·18	3·81	29·0	76·5	24	31·0		
13 ..	8	9·1%	0	8·5	2·38	23·0	99	37	37·0	0·76	0·42
		6th day	12	11·2	3·60	33·0	91	31	34·0		
14 ..	10	13·0%	0	3·4	1·28	9·0	70	26	38·0	1·30	0·65
		9th day	12	6·8	2·10	18·0	90	32	38·0		
15 ..	10	11·5%	0	3·4	1·50	15·0	100	23	23·0	0·60	0·60
		7th day	24	10·0	3·78	28·0	80	26	35·0		
16 ..	8	15·1%	0	2·0	0·65	8·5	130·7	30	23·5	0·70	0·80
		10th day	32	10·0	3·90	36·0	92	26	28·0		
17 ..	4	22·5%	0	6·8	2·10	21·0	100	32	32·0	0·77	0·47
		7th day	20	13·26	4·50	40·0	90	30	33·0		
18 ..	5	17·5%	0	6·4	2·00	19·5	97·5	32	32·0	1·25	0·50
		7th day	15	11·28	4·50	35·0	77	25	32·0		
19 ..	2	13·5%	0	6·8	2·00	20·0	100	34	34·0	0·58	0·50
		6th day	30	11·5	4·50	35·0	77	25	32·0		
20 ..	4	15·3%	0	3·4	1·55	15·0	99	22	22·0	0·37	0·61
		9th day	30	10·5	3·10	29·0	96	34	36·0		
21 ..	10	14·1%	0	2·7	1·0	10·0	100	27	27·0	0·75	0·72
		7th day	26	10·8	3·80	33·0	87	28	33·0		

TABLE II.—*Plasma-protein Levels in Cases Treated with Vitamin B_{12}*

Case No.	Body Weight (lbs.)	Home Diet. Prot. and Cal. Intake/day	Hosp. Diet. Prot. and Cal. Intake/day	Protein			
				Total (g./100 ml.)	Albumin (g./100 ml.)	Globulin (g./100 ml.)	A/G Ratio
1 ..	—	Prot. 38 g. Cal. 800	Prot. 68·2 g. Cal. 1,600	4·30	1·90	2·40	0·8 : 1
				5·08	3·63	1·45	2·5 : 1
2 ..	—	Prot. 32 g. Cal. 848	Prot. 68 g. Cal. 1,633	4·39	2·08	2·31	0·9 : 1
				4·55	2·85	1·70	1·6 : 1
3 ..	93	Prot. 28 g. Cal. 720	Prot. 71 g. Cal. 1,771	6·08	1·80	4·28	1 : 2·6
				7·00	3·80	3·20	1·2 : 1
4 ..	85	Prot. 32 g. Cal. 848	Prot. 69 g. Cal. 1,664	4·10	2·00	2·10	1 : 1
				—	—	—	—
5 ..	75	Poor intake due to diarrhoea	Prot. 74 g. Cal. 1,684	6·20	1·48	4·72	1 : 3
				—	—	—	—
6 ..	—	,, ,,	Prot. 89 g. Cal. 2,284	5·25	2·80	2·45	1·2 : 1
				6·30	4·00	2·30	1·7 : 1
7 ..	81	,, ,,	Prot. 71 g. Cal. 1,771	3·67	2·40	1·27	1·8 : 1
				5·20	2·80	2·40	1·2 : 1
8 ..	92	,, ,,	Prot. — Cal. —	3·28	1·99	1·29	1·5 : 1
				—	—	—	—
9 ..	88	Prot. 36 g. Cal. 784	Prot. 89 g. Cal. 2,176	3·80	1·30	2·50	1 : 1·7
				5·90	2·90	3·00	1 : 1
10 ..	107	Prot. 35 g. Cal. 840	Prot. 68 g. Cal. 1,839	3·30	1·30	2·00	1 : 1·5
				6·30	3·90	2·40	1·6 : 1
11 ..	85	Prot. 42 g. Cal. 1,081	Prot. 71 g. Cal. 1,811	4·48	2·10	2·38	1 : 1·1
				6·10	4·10	2·00	2 : 1
12 ..	107	Prot. — Cal. —	Prot. 68 g. Cal. 1,771	3·30	1·30	2·00	1 : 1·5
				6·80	3·40	3·40	1 : 1
13 ..	91	Prot. 68 g. Cal. 1,687	Prot. 68 g. Cal. 1,687	8·10	3·90	4·20	1 : 1·1
				6·80	5·30	1·50	3·5 : 1
14 ..	—	Prot. — Cal. —	Prot. 59 g. Cal. 1,545	4·90	2·10	2·80	1 : 1·3
				—	—	—	—
15 ..	93	Prot. 63 g. Cal. 1,727	Prot. 63 g. Cal. 1,727	7·00	2·70	4·30	1 : 1·6
				6·70	4·00	2·70	1·5 : 1
16 ..	—	Prot. 77 g. Cal. 1,152	Prot. 82·5 g. Cal. 1,990	4·70	2·60	2·10	1·2 : 1
				6·80	5·30	1·50	3·5 : 1
17 ..	—	Prot. — Cal. —	Prot. 78·5 g. Cal. 1,930	3·40	2·40	1·00	2·4 : 1
				8·40	5·30	3·10	1·7 : 1
18 ..	135	Prot. 37·5 g. Cal. 778	Prot. 83 g. Cal. 1,795	6·41	4·01	2·40	1·6 : 1
				6·80	5·10	1·70	3 : 1
19 ..	—	Prot. 32 g. Cal. 848	Prot. 59 g. Cal. 1,545	4·20	1·60	2·60	1 : 1·6
				6·90	2·50	4·40	1 : 1·7
20 ..	—	Prot. 37·5 g. Cal. 778	Prot. 76 g. Cal. 1,871	4·10	2·60	1·50	1·7 : 1
				5·80	3·20	2·60	1·2 : 1
21 ..	103	Prot. 32 g. Cal. 848	Prot. 63 g. Cal. 1,701	6·70	2·40	4·30	1 : 1·8
				7·80	4·00	3·80	1·1 : 1

Methods

All the patients were in hospital during the period of treatment. They were given no other treatment than vitamin B_{12}. A history of their illness and details of their diet during the previous six months were recorded. Each case was given a thorough examination. Full blood counts; total and differential blood proteins; urine, stool, and gastric analyses; and a blood Kahn test or Wassermann reaction were carried out. Bone marrow was megaloblastic in all cases. The reticulocyte count was done daily from the time of admission until 15 days after the initiation of treatment. When the blood level had become stationary, treatment with vitamin B_{12} was given. Most patients came to the hospital in a low condition, and, as they had had no previous therapy, treatment was instituted after the first blood examination. Vitamin B_{12} was given intramuscularly in 20-μg. doses either every other day or every fifth day, depending upon the condition of the patient (Tables I and II).

All patients were females and did household duties. Their ages varied between 19 and 45 years—the child-bearing age—15 of them being between 19 and 30. The actual distribution is given in Table III.

TABLE III.—*Age Distribution*

Age in Years	No. of Cases
10–19	1
20–29	10
30–39	9
40–45	1
Total	21

Five of the 21 patients were admitted in the third trimester of pregnancy. Eleven were treated within a period of three months after delivery—nine of these within 15 days of delivery. Treatment of one of the five cases of pregnancy was continued during the puerperium.

The remaining five patients had a history of frequent attacks of diarrhoea and poor nutrition. One of them had bleeding haemorrhoids. Nine cases had macrocytic hypochromic anaemia and 11 had macrocytic normochromic anaemia—types common in this part of the country. The initial erythrocyte level was below 1,000,000 in four cases, below 1,500,000 in eleven, below 2,000,000 in two, and below 2,500,000 in four. The haematological findings before and after treatment are given in Table IV.

TABLE IV.—*Haematological Findings Before and After Treatment*

	Haemoglobin (g./100 ml.)		R.B.C. (mil./c.mm.)		C.V. %	
	Before	After	Before	After	Before	After
Mean	4·01	9·82	1·35	3·58	13·1	28·7
Maximum ..	8·5	13·3	2·38	4·8	23·00	40·0
Minimum ..	2·0	5·0	0·65	1·2	8·50	12.0

The total proteins, particularly albumin, in all cases were low, and although the values increased with treatment they did not reach a normal level (Table II). This hypoproteinaemia was associated with oedema of the feet in 15 patients. Reticulocytosis occurred in all cases after treatment, and varied between 3.5 and 25%; the maximum reticulocytosis usually occurred between the seventh and tenth days. In some cases it was delayed.

Twenty cases responded adequately to treatment with vitamin B_{12}. One (Case 4) of these was given a mixture containing iron and ammonium citrate—90 gr. (5.9 g.) a day—during the third week of treatment. The response seemed to be better with iron. Megaloblasts were present in the bone marrow, but the peripheral blood picture was hypochromic. Another patient (Case 5), who had soreness of tongue and marked diarrhoea, gave a poor haematological response to vitamin B_{12} (60 μg. in 15 days), though there was a general improvement and the oedema disappeared on the fourth day. The maximum reticulocyte count was 3.5% on the fourth day. Later she responded very rapidly to parenteral folic acid. In most cases the treatment was given throughout the stay in hospital and lasted 12 to 54 days. In some it was given on alternate days or every fourth, seventh, or tenth day, depending upon the severity of the condition. The minimum amount used was 60 μg. in 15 days, and the maximum 360 μg. in 53 days.

Roughly, it can be deduced that in mild cases an average of 4 μg. a day was needed to produce improvement, and in severe cases as much as 10 μg. a day. It was also found that anaemias associated with pregnancy required higher doses.

Discussion

The place of vitamin B_{12} in the treatment of macrocytic anaemia in the Tropics is still unsettled (Dameshek, 1949; Minot and Castle, 1950). The suggestion that it could not be effective resulted from an old-standing conception that refined liver extract had little effect. It was taken for granted that vitamin B_{12} was the most active substance in the refined liver extract. Patel and Bhende (1949), however, showed that refined liver extract gave good results in a large number of cases of tropical macrocytic anaemia. Sometimes only small doses were required. In their report the requirement in tropical macrocytic anaemia was two or three times that in Addisonian pernicious anaemia. It was also shown (Patel, 1948; Patel and Kocher, 1950; Patel, 1950) that vitamin B_{12} was efficacious in tropical macrocytic anaemia and pregnancy anaemia in doses larger than that required in Addisonian pernicious anaemia. The results of the present investigation also show that vitamin B_{12} is effective in megaloblastic anaemia of pregnancy and the puerperium as it occurs in India, and in four cases of tropical macrocytic anaemia occurring in women, but that higher doses are required than in pernicious anaemia.

In one woman suffering from tropical macrocytic anaemia the haematological response with vitamin B_{12} was not satisfactory, even though there was general improvement, with disappearance of oedema. This patient later responded to parenteral folic acid therapy. Such cases have also been noted by Das Gupta *et al.* (1949). Other cases which had initially failed to respond to folic acid subsequently responded to liver extract.

From all available evidence it can be concluded that vitamin B_{12} is effective in most cases of tropical megaloblastic anaemia and megaloblastic anaemia of pregnancy and the puerperium, but that the dosage required is higher than is needed in Addisonian pernicious anaemia. Our results confirm those reported by Patel and his co-worker.

Summary

Sixteen cases of megaloblastic anaemia of pregnancy and the puerperium were treated successfully with parenteral vitamin B_{12}.

Out of five cases of tropical megaloblastic anaemia treated with vitamin B_{12}, four responded to vitamin B_{12} and one responded better to subsequent folic acid therapy.

Four micrograms of vitamin B_{12} a day was the estimated requirement in mild cases of macrocytic anaemia of pregnancy and 10 µg. in severe cases.

I wish to thank the Glaxo Laboratories (India) Ltd. for supplying vitamin B_{12}; Dr. J. C. Patel for his valuable help; and Dr. S. Swarup for her assistance.

REFERENCES

Berk, L., Denny Brown, D., Finland, M., and Castle, W. B. (1948). *New Engl. J. Med.*, **239**, 328.
Bethell, F. H., Meyers, M. C., and Neligh, R. B. (1948). *J. Lab. clin. Med.*, **33**, 1477.
Dameshek, W. (1949). *Blood*, **4**, 76.
Das Gupta, C. R. (1950). Remarks in discussion at International Congress of Haematology, Cambridge.
—— Chatterjea, J. B., and Mathen, K. K. (1949). *Indian J. med. Res.*, **37**, 455.
Day, L. A., Hall, B. E., and Pease, G. L. (1949). *Proc. Mayo Clin.*, **24**, 149.
Hall, B. E., and Campbell, D. C. (1948a). Ibid., **23**, 584.
—— —— (1948b). Ibid., **23**, 591.
Minot, G. R., and Castle, W. B. (1950). *The 1949 Year Book of Medicine*, p. 375. Year Book Publishers, Chicago.
Patel, J. C. (1948). *British Medical Journal*, **2**, 934.
—— (1950). "Vitamin B_{12} in Tropical Macrocytic Anaemia." Paper read at International Congress of Haematology, Cambridge. (To be published.)
—— and Bhende, Y. M. (1949). *Blood*, **4**, 259.
—— and Kocher, B. R. (1950). *British Medical Journal*, **1**, 924.
Spies, T. D., Lopez, G. G., Milanes, F., Toca, R. L., and Cilver, B. (1948a). *Sth. med. J.*, **41**, 523.
—— Stone, R. E., and Armaburu, T. (1948b). Ibid., **41**, 522.
—— Suarez, R. M., Lopez, G. G., Milanes, F., Stone, R. E., Toca, R. L., Armaburu, T., and Kartus, S. (1949). *J. Amer. med. Ass.*, **139**, 521.
Ungley, C. C. (1948a). *Lancet*, **1**, 771.
—— (1948b). *British Medical Journal*, **2**, 154.
West, R. (1948). *Science*, **107**, 398.

AN OUTBREAK OF RESPIRATORY TUBERCULOSIS IN A SCHOOL

BY

R. T. BEVAN, M.B., B.Ch., D.P.H., B.Sc.
Deputy County Medical Officer, Glamorgan County Council; Lecturer in Preventive Medicine, Welsh National School of Medicine

P. T. BRAY, M.B., M.R.C.P., D.C.H., B.Sc.
Paediatrician, United Cardiff Hospitals and Welsh Regional Hospital Board; Lecturer in Paediatrics, Welsh National School of Medicine

AND

J. F. HANLY, M.B., B.Ch., D.P.H.
Assistant Chest Physician, Pontypridd and Rhondda Hospital Management Committee

At a time when medical and lay opinion is being focused on the problem of tuberculosis it is opportune to relate the story of a local outbreak. Criticism is often directed at the difficulties associated with the threefold control of our Health Service. It is suggested that there should be a greater integration of the hospital, general practitioner, and preventive medicine services. Tuberculosis is frequently cited as an example of a disease which could be combated more effectively if a closer liaison existed between the various services. The localized outbreak to be described is therefore not only of clinical but also of medical administrative interest.

The first intimation of this outbreak followed an observation by the paediatrician who was investigating three cases of clinical primary respiratory tuberculosis in hospital and, in addition, had made domiciliary visits to two similarly affected children. Noting that they all came from the same area, he informed the County Medical Officer on July 15, 1950. It was quickly confirmed that all the affected children attended the same school, and the school became the centre of investigations. Inquiries revealed that a member of the teaching staff had been absent from May 23 to June 26 suffering from laryngitis, but on July 17, when the school was visited by the Deputy County Medical Officer, this teacher was again absent, this time with "haemoptysis," which had occurred on the previous Friday (July 14). In due course the diagnosis of respiratory tuberculosis was confirmed.

As a routine the milk supplies at the homes of the affected children were investigated. There was no common supply. The school milk supply was pasteurized and there was no record of inefficient heat treatment.

Future action was decided at a meeting of the paediatrician, the local chest physician, and the County and Deputy County Medical Officers. A letter was sent to the parents of all the children at the school asking their consent to carry out Mantoux skin tests on the children. In addition, the health visiting staff of the local health authority called at the homes of all the children who were absent from school, and arrangements were made for them to be investigated. It was then possible to test immediately 176 of the 186 children on the school register. This excellent co-operation of the parents reflects their keen interest in the medical welfare of their children. Those found to be Mantoux-positive were *x*-rayed, using large films. The results of the Mantoux tests and *x*-ray examination are set out in Table I. Mantoux testing consisted in the intradermal injection of 0.1 ml. 1/10,000 old tuberculin followed by 0.1 ml. 1/100 in the negatives.

TABLE I.—*July Mantoux and X-ray Tests*

(a) Results in Various Ages

Age	No. Tested	Mantoux-positive	Percentage Positive	No. with *X*-ray Evidence of Tuberculosis
5	17	3	18	1
6	30	9	30	3
7	20	7	35	1
8	20	6	30	0
9	16	7	44	2
10	19	5	26	1
11	22	4	18	0
12	10	4	40	0
13	14	5	36	0
14	8	2	25	0
Total	176	52	30	8

The above figures include the five cases which were already undergoing treatment.

(b) Results in Various School Classes

Class	Age Range	No. Tested	Mantoux-positive	Percentage Positive	No. with *X*-ray Evidence of Tuberculosis
Infants ..	5–7	48	13	27	4
Standards I and II ..	6–9	31	8	26	1
Standard III	8–11	26	12	46	2
Standard IV	9–12	33	8	24	1
Forms I and II ..	11–14	38	11	29	0
Total ..	—	176	52	30	8

The schoolteacher who was now the suspected source of infection was in charge of Standard III. Why, then, should the infants' class show the greatest incidence of cases with *x*-ray evidence of tuberculosis? The explanation was apparent when it was discovered that this teacher was in charge of the infants' class from May 8 to 12 owing to the temporary absence of the infants' class teacher.

The return to teaching duties following the initial period of sickness was unfortunate, since it was probable that further children were infected during this period. It was essential, therefore, to repeat the routine tests when the children returned to school after their summer vacation, as by that time the Mantoux test would have had time to show conversion. The local general practitioners were kept fully informed of the position, so that when children presented suspicious symptoms they were referred immediately to the local chest clinic. During the school vacation additional cases were brought to light in this manner.

One of the difficulties was to avoid undue alarm, and, after a local request, the parents were given an opportunity to be present at a meeting in the school. This had the effect of diminishing the natural anxiety of parents, and, incidentally, was a means of health education of the general public. The school premises were disinfected during the holidays in addition to the normal holiday "spring clean." It is doubtful whether this action was scientifically necessary, but it had a considerable psychological effect.

In November all those children who were Mantoux-negative in July or who had not been previously tested were asked to submit to investigation. With few exceptions the parents were prepared to co-operate. The results obtained are set out in Table II.

TABLE II.—*Mantoux State in November and X-ray Results*

(a) By Age

Age	(i) Negative Mantoux in July			(ii) Tested for First Time		
	No. Tested	Mantoux-positive	X-ray Evidence of Tuberculosis	No. Tested	Mantoux-positive	X-ray Evidence of Tuberculosis
5	13	0	0	1	1	0
6	19	1	0	0	0	0
7	12	1	0	1	1	0
8	14	5	3	2	2	0
9	9	2	1	2	0	0
10	14	1	0	0	0	0
11	18	2	0	0	0	0
12	6	0	0	0	0	0
13	8	0	0	1	1	0
14	4	0	0	1	0	0
Total ..	117	12	4	8	5	0

(b) By Class

Class	(i) Negative Mantoux in July			(ii) Tested for First Time		
	No. Tested	Mantoux-positive	X-ray Evidence of Tuberculosis	No. Tested	Mantoux-positive	X-ray Evidence of Tuberculosis
Infants ..	32	1	0	1	1	0
Standards I and II	22	2	0	2	2	0
Standard III ..	14	8	4	2	1	0
Standard IV ..	25	0	0	1	0	0
Forms I and II	24	1*	0	2	1	0
Total ..	117	12	4	8	5	0

These figures include children who were referred to the chest clinic during the school vacation.

* This child manifested erythema nodosum in August, but showed no abnormal radiological picture.

Reference to Table II (*b*) shows that no fewer than 8 of the 14 children in Standard III who were negative in July had by November converted. Table III emphasizes the abnormal picture of this class—the class whose teacher had developed pulmonary tuberculosis.

Although the numbers are small it is of interest to record the Mantoux state by age in this school and to compare the figures with routine Mantoux testing of schoolchildren in the Maesteg area, which had been undertaken by the Mass Radiography Unit of the Welsh Regional Hospital Board in 1949. Maesteg is an area which is comparable to the area under review.

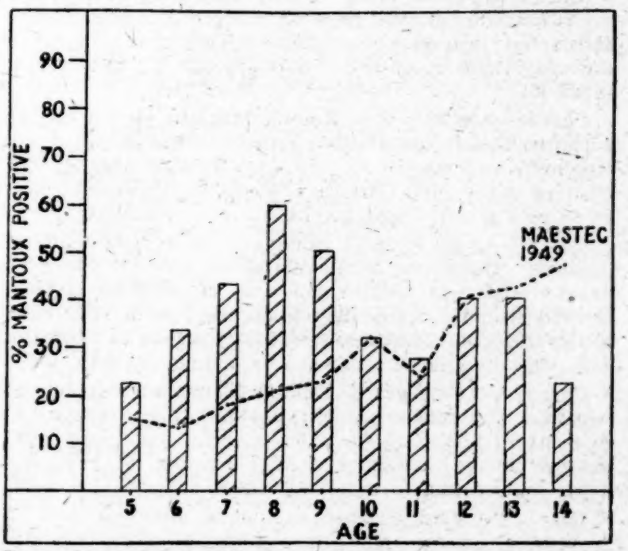
TABLE III.—*Mantoux State of Pupils at Completion of Investigations*

Class	No. Tested	Mantoux-positive	% Positive	X-ray Evidence of Tuberculosis
Infants ..	49	15	30·6	4
Standards I and II	33	12	36·4	1
Standard III ..	28	21	75·0	6
Standard IV ..	34	8	23·5	1
Forms I and II ..	40	13	32·5	0
Total ..	184	69	—	12

TABLE IV

Age	School Under Review			Maesteg Valley		
	No.	Mantoux-positive	% Positive	No.	Mantoux-positive	% Positive
5	18	4	22·2	209	30	14·4
6	30	10	33·3	235	30	12·8
7	21	9	42·9	286	50	17·5
8	22	13	59·1	269	55	20·5
9	18	9	50·0	289	65	22·5
10	19	6	31·6	262	83	31·7
11	22	6	27·3	293	70	23·9
12	10	4	40·0	256	103	40·2
13	15	6	40·0	203	86	42·4
14	9	2	22·2	220	105	47 7

The differences for ages 6, 7, 8, and 9 are of statistical significance.



Comparison of tuberculin sensitivity at the school with the Maesteg Survey, 1949.

Case Records

The clinical histories of the twelve children affected are as follows :

Case 1.—Aged 5½ years. Admitted to hospital on June 29 with history of tonsillitis four weeks previously. On June 21 became generally unwell and had clinical signs of erythema nodosum. This was followed by a persistent pyrexia. Investigations showed the Mantoux test to be positive 1/1,000, and *x*-ray of chest revealed enlargement of glands at the right hilum. In December, 1950, this child developed collapse of lower lobe of the right lung, but by February the condition was resolving satisfactorily.

Case 2.—Aged 10 years. Admitted to hospital on July 8, having been ill at home since June 29 with a pyrexia for which no adequate cause could be found. A Mantoux test was positive, and investigation showed enlarged glands at the left hilum. By February this child was fit enough to return to school.

Case 3.—Aged 6 years. Admitted to hospital on July 4, having had scarlet fever and chicken-pox a month previously, from which she appeared to make a good recovery. Since June 25 she had a pyrexia of unknown origin. The Mantoux test was positive and there was enlargement of glands at the left hilum with an opacity in left lower zone. The glandular enlargement subsided satisfactorily, and it was estimated that the child would be fit to return to school in March, 1951.

Case 4.—Aged 6 years. History of measles in mid-June, followed by a normal recovery, but on July 4 a pyrexia developed. Investigation showed enlarged right hilar glands and a positive Mantoux reaction. *X*-ray examination in January, 1951, showed the primary focus to be cleared, but enlarged hilar glands were still present.

Case 5.—Aged 7 years. History of pyrexia starting on July 4. Investigation showed enlargement of the glands at the bifurcation of the trachea and a positive Mantoux reaction. By February the lesion had cleared completely and her general condition was satisfactory.

Case 6.—Aged 6 years. Routine Mantoux test positive. X-ray examination of chest revealed enlarged left hilar glands. Progress was such that this boy was allowed to attend school in December.

Case 7.—Aged 9 years. Routine Mantoux test positive. *X*-ray examination of chest showed left hilar glands enlarged with stippling in left mid-zone. Satisfactory resolution of root glands enabled her to start school in February, 1951.

Case 8.—Aged 9 years. Vague history suggestive of erythema nodosum. Routine Mantoux test positive. *X*-ray examination of chest revealed enlarged right hilar glands. Satisfactory resolution was made by February, 1951, when she was able to be up and about, although not fit to return to school.

Case 9.—Aged 8 years. Routine Mantoux test on July 21 negative. General malaise and pyrexia on July 28. Mantoux test positive on August 18, and *x*-ray films of chest showed enlarged right hilar glands. Satisfactory resolution was made by February and the child was fit to return to school.

Case 10.—Aged 9 years. Routine Mantoux test on July 21 negative. Developed febrile illness on July 31, when the Mantoux test was positive and *x*-ray examination of chest showed shading in the right upper zone with right hilar glands enlarged. There was satisfactory healing by February, 1951, and the child was able to carry on normal activities.

Case 11.—Aged 8 years. Routine Mantoux test on July 21 negative. Referred to clinic, and Mantoux test repeated in September; the test was then positive, and *x*-ray films showed enlarged left hilar glands. Progress by February, 1951, enabled him to return to school.

Case 12.—Aged 8 years. Routine Mantoux test in November positive and *x*-ray films of chest revealed enlargement of right hilar glands. Satisfactory progress was made, enabling her to be fit for school in February, 1951.

In all cases the treatment consisted only of rest in bed, at home or in hospital, with clinical and radiological supervision. Streptomycin was not given.

All the teaching and non-teaching staff of the school immediately volunteered to undergo *x*-ray examinations, and, apart from the affected teacher, none showed evidence of active tuberculosis.

Conclusions

The staffs of hospitals and local authorities, together with general practitioners, must co-operate in providing a comprehensive health service in which therapeutic and preventive measures play equally important parts.

This local outbreak is an example of the danger that a teacher suffering from pulmonary tuberculosis can be to schoolchildren. The favourable outcome in this series does not detract from the need for preventive measures. Periodic compulsory *x*-ray examinations seem to offer the most practicable solution. It must be remembered, however, that pulmonary tuberculosis may be rapidly progressive in a young adult and that annual examinations may not be a sufficient safeguard. Some, maybe, would argue that six-monthly routine examinations would involve waste of effort and money, but, on the other hand, outbreaks such as the one described may be prevented. Preventive measures, we submit, are in the long run financially economical, in addition to being sound from a purely medical standpoint.

The histories suggest an incubation period between the limits of 40 and 62 days.

Summary

Five cases of clinical primary respiratory tuberculosis were reported in pupils of the same school. The probable source of infection was traced to a schoolteacher. Immediate Mantoux and *x*-ray testing revealed three further cases. The return of the teacher concerned to school after a short period of absence necessitated a follow-up examination of the pupils, and four further cases were brought to light. The classes predominantly affected were those with which the teacher had come into closest contact.

We wish to acknowledge the active part played by Dr. W. E. Thomas, the County Medical Officer, and Dr. J. G. Cox, the chest physician, in the investigations and control of this outbreak.

THE SURGERY OF PAROTID TUMOURS

EXPOSURE OF MAIN TRUNK OF FACIAL NERVE

BY

H. S. SHUCKSMITH, F.R.C.S.

T. McM. BOYLE, F.R.C.S., D.L.O.

AND

W. K. J. WALLS, M.B., Ch.B.

(From the Departments of Surgery, E.N.T., and Anatomy, University of Leeds)

Exposure of the main trunk of the facial nerve and the dissection of the distal branches and filaments form the method we have evolved for the removal of parotid tumours.

Willis (1948, 1950), from whose writings we quote, classifies epithelial salivary-gland tumours as follows: simple adenoma; pleomorphic adenomas and adenocarcinomas (so-called mixed parotid tumours); anaplastic carcinomas; and adenolymphomas (papillary cystadenomas). He states that 90% of all salivary tumours fall into the group of pleomorphic adenomas, and that while most of these tumours grow slowly and appear to be well circumscribed they are not strictly benign. He further states that the mode of origin of the tumours parallels that of mammary carcinoma, which often arises from a considerable field of mammary epithelium. He believes that the recurrence rate after inadequate operation may be as large as 62%, and that the principal factor is the conservative type of operation used because of fear of damage to the facial nerve.

He mentions, too, quoting Patey, that the recurrence may arise from small satellite tumours independent of the main one.

The incidence of parotid tumours, other than pleomorphic adenomas, makes any other clinical diagnosis than this unwise (except the obvious cancer), and their pathology demands that any surgical treatment should be wide excision.

McKenzie (1948) has reiterated that Bailey (1948) is inaccurate in his description of the gland as a bilobed structure. We have not found Bailey's analogy of the facial nerve as the filling in a parotid sandwich of any value in removing parotid tumours, but our experience of facial-nerve branches and filaments makes us accept McKenzie's analogy of the parotid growing like a creeper, weaving itself into the meshes of a trellis-work fence (the facial nerve). Kidd (1950) has described identification of the cervical branch of the facial nerve in the submaxillary triangle as the first step to preserve all the facial nerve. From dissections, however, this nerve appears small and might be difficult to find. One of us (W. K. J. W.) has noted that it commonly lies deep to the platysma $\frac{3}{8}$ in. (1 cm.) behind the angle of the jaw, but this is inconstant.

Method

It seemed to one of us (H. S. S.) that the sensible method to preserve the facial nerve and yet, without reservation, resect widely any superficial parotid tumour would be to expose first the main trunk of the facial nerve soon after its emergence from the stylomastoid foramen and then from this large strong trunk to work forward to the main divisions and filaments as need be. This idea is the basis of the method we describe.

FIG. 1.—Photograph of exposed left side of face.

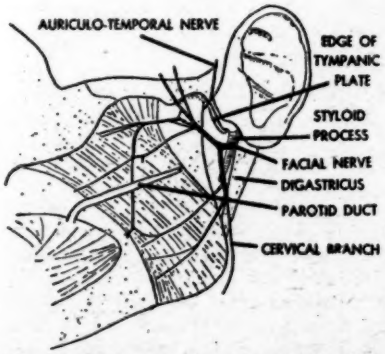


FIG. 2.—Diagram of exposed left side of face.

The facial-nerve trunk runs $\frac{1}{4}$ in. (0.6 cm.) below the free edge of the tympanic plate, as determined by one of us (T. McM. B.), and the exposure of the free edge of the tympanic plate is the key to the operation (see Figs. 1 and 2).

The parotid and temporo-mandibular regions are infiltrated with local analgesic to help haemostasis. The incision is liberal, extending from Macewen's triangle a fingerbreadth behind the pinna and just below the external auditory meatus down to the lower border of the mandible; flaps are dissected. The outer border of the tympanic plate is exposed and the main trunk of the nerve found $\frac{1}{4}$ in. (0.6 cm.) below; the nerve is dissected anteriorly, and in this forward sweep there is no confusion between fine filaments of nerve, fibrous tissue septa, and tiny ducts. The tumour is now excised widely, and after haemostasis the wound is closed with an intracuticular stitch and drained.

We first performed the operation on September 20, 1950, on a woman aged 70. Our clinical diagnosis was an encapsulated parotid tumour, but histology showed a carcinoma—a fitting confirmation of Willis's description of the pathology of these tumours and apt support for our thesis of wide safe removal.

Summary

A new method of surgical treatment of parotid tumours is described.

The main trunk of the facial nerve is exposed $\frac{1}{4}$ in. (0.6 cm.) below the free outer border of the tympanic plate as the first step in the operation to excise widely the tumour and yet preserve the nerve.

REFERENCES

Bailey, H. (1948). *British Medical Journal*, **2**, 245.
Kidd, H. A. (1950). Ibid., **1**, 989.
McKenzie, J. (1948). *J. Anat., Lond.*, **82**, 183.
Willis, R. A. (1948). *Pathology of Tumours*. Butterworth, London.
—— (1950). *Principles of Pathology*. Butterworth, London.

Medical Memoranda

A Relaxant of Very Brief Action

A recent important paper (Paton and Zaimis, 1950) pointed out that the myoneural blocking agents in clinical use as relaxants could be classified, according to their mode of action, into two groups: (1) true curarizing agents—e.g., D-tubocurarine chloride; (2) depolarizing agents, of which group decamethonium iodide is the only member in common use. The different properties of these agents in anaesthetic practice have recently been reviewed (Scurr, 1951).

Bovet (1949) has reported an extensive pharmacological investigation of a large number of synthetic "curarizing" agents. One of these compounds, closely related to succinyl-choline and designated 362 I.S., was considered suitable for clinical trial, and Valdoni (1949) reported briefly on its use in a small number of cases. This substance is di-(β-ethyldimethyl-ammonium-ethyl) succinate diiodide, and belongs to the depolarizing group of agents. Recently a small supply (4 g.) of this drug became available, and it has been possible to test its effect in a small series of cases.

Effects

After the rapid injection of 50–75 mg. into the average adult the first signs are evident in about 20 seconds. The onset of muscular paralysis is marked by transitory tremors and flickering of muscles similar to but more pronounced than those noted with decamethonium iodide. After 30–40 seconds the effect of voluntary muscular paralysis is maximal, and complete respiratory paralysis may occur. Recovery takes place approximately two minutes from the time of injection, full respiratory activity being rapidly regained. In no case has the duration of paralysis exceeded 2½ minutes.

In view of this extremely brief duration of action, great precision in dosage is neither possible nor necessary, and one aims at giving a fully adequate dose. No significant circulatory changes or other side-effects have been observed.

Endotracheal Intubation

The agent has been used for this purpose in 20 cases, the technique being as follows : 10 ml. of 5% thiopentone is injected and followed by 75 mg. of the drug; after a pause of 30–40 seconds, during which oxygen may be administered, intubation is performed.

In all cases satisfactory conditions for intubation have been obtained. In view of the very evanescent relaxation, it is essential to carry on promptly with an inhalation anaesthetic after the intubation; a supplement such as pethidine enables the endotracheal tube to be well tolerated in the light plane of anaesthesia.

Electric Convulsion Therapy

The ideal relaxant for the attenuation of electrically induced convulsions should have a very brief action so as to ensure prompt recovery, avoid the dangers of prolonged respiratory depression, and reduce the amount of skilled supervision required afterwards.

362 I.S. has been used on 18 occasions for this purpose. It has been possible to ensure attenuation in the highest degree, and yet in every case to have full respiratory activity present within 2½ minutes from the start of the injection. It had been hoped that, in view of the very rapid action of the drug, the subjective feelings of fear and suffocation which accompany curarization in the conscious state might be avoided and render unnecessary the use of an accompanying dose of barbiturate. Unfortunately this is not the case, but it is possible to reduce greatly the dose of thiopentone. As a result of the rapid recovery from the relaxant and the small dosage of barbiturate, the patients become ambulant very much earlier than with any other method.

The technique used is as follows : 75 mg. of 362 I.S. is injected rapidly intravenously and is promptly followed by 3–4 ml. of 5% thiopentone. There follows a pause, during which oxygen may be administered, until 40 seconds have elapsed from the start of injection; the electric convulsion is then induced.

Other Uses

The duration of action of this relaxant is obviously too short to meet the surgeon's requirements. It might be useful, possibly in repeated doses, to facilitate peritoneal closure. Theoretically it might be possible to prolong the paralytic effect by administering the drug combined with neostigmine. In view of the small supplies available, it has not been possible to explore these methods of using this relaxant; however, it does seem to be ideal for the attenuation of electrically induced convulsions, and further investigation along these lines seems highly desirable.

I am indebted to Dr. Gerald Garmany and Dr. Audrey Ferguson, of the Psychiatric Department, for co-operation, and to Dr. J. H. W. Smith for valuable assistance.

C. F. Scurr, M.B., D.A.
Department of Anaesthetics, Westminster Hospital.

References

Bovet, D. (1949). *R.C. Ist. sup. Sanità*, **12**, 180.
Paton, W. D. M., and Zaimis, E. J. (1950). *Lancet*, **2**, 568.
Scurr, C. F. (1951). *Brit. J. Anaesth.*, **23**, 103.
Valdoni, P. (1949). *R.C. Ist. sup. Sanità*, **12**, 255.

Acute Intestinal Obstruction from Foreign Bodies

The following two cases of intestinal obstruction may be found of interest.

Case 1

A married woman aged 73 had a history of attacks of recurrent acute cholecystitis. On October 15, 1947, cholecystostomy was performed for localized abscess secondary to perforation of the gall-bladder. Further attacks of acute cholecystitis occurred, and on October 12, 1949, the previous scar was excised, cholecystectomy performed, and a catheter passed down the common bile duct into the duodenum. There was free oozing from the gall-bladder bed, into which was placed an "oxycel" pack. The wound was closed, with drainage. There was some mild post-operative wound infection; this subsided, and she was discharged on November 9.

On November 19 the patient was readmitted as an emergency, suffering from acute intestinal obstruction. On November 21 operation was performed by Mr. A. York Mason. The small bowel was acutely distended, and there was an obstruction 3 in. (7.5 cm.) from the ileo-caecal valve consisting of a putty-like tumour, about 4 in. (10 cm.) long, within the lumen of the bowel. The bowel was incised and a rolled pack of oxycel removed. The bowel was sutured.

The patient made an uninterrupted recovery, and was discharged on December 14.

Comment.—The oxycel pack which had been inserted to the gall-bladder bed 38 days previously had evidently ulcerated through the duodenum and caused obstruction in the terminal ileum. Examination of the pack showed that there had been practically no absorption, and I believe that the use of these packs in situations in which they cannot be removed is contraindicated.

Case 2

A married woman aged 65 had had bilious attacks since 1939, and was seen in the out-patient department on November 17, 1950. There was some tenderness in the epigastrium, and the cholecystogram failed to outline the gall-bladder.

On December 22 the gall-bladder was explored and appeared to be normal. The duodenum was incised and a mass of plum-skins, 2 in. (5 cm.) in length and 1 in. (2.5 cm.) in diameter, was found adherent to the walls and blocking the second part of the duodenum. The duodenum was sutured and abdomen closed.

The patient made an uninterrupted recovery and was discharged on January 10, 1951.

The specimen consisted of a mass of rolled-up plum-skins in which some incrustation had occurred.

Comment.—The second part of the duodenum was rather short, and the junction of the second and third parts of the duodenum was rather more prominently curved than normal, so that the mass of plum-skins had been unable to pass into the third part of the duodenum, giving rise to symptoms simulating chronic cholecystitis.

H. A. Kidd, F.R.C.S.Ed., M.R.C.O.G.,
Consultant Surgeon, St. Helier Hospital, Carshalton, Surrey.

The house governors and matrons of a number of hospitals in Suffolk have been told that they must not economize by diluting milk (*Daily Telegraph*, September 25). As soon as it was learnt that this was being done the local hospital management committee instructed them to "effect alternative economy." The chairman assured the committee that, whatever else they saved money on, they would not do it by cutting down on food.

Reviews

YELLOW FEVER

BY

Sir RICKARD CHRISTOPHERS, F.R.S.

Yellow fever appears first to have been recognized as a disease entity in the seventeenth century. It has always been popularly considered an American disease, but it may have been originally introduced from Africa. As "yellow jack" it was in the early days of shipping a terror to sailors and a threat to ports and shipping throughout the tropical world. It has now been virtually abolished in its urban epidemic form even from areas where it was once prevalent, and with due precautions it is no longer any threat to shipping or to other countries. This virtual conquest of a deadly disease has been possible through the discovery in 1901 by the U.S. Yellow Fever Commission in Cuba that the disease was transmitted by the mosquito now known as *Aëdes aegypti*, and to a considerable extent to the demonstration by General Gorgas at Panama that yellow fever could be controlled by measures directed against this mosquito and protection of man from its bites.

The story of these events half a century ago is still one of the epics in the history of medicine, and many will enjoy reading in the recently published biography of General William C. Gorgas,[1] by John M. Gibson, the interesting intimate account there given of the life and work of Gorgas and of the circumstances under which the United States Yellow Fever Commission worked in Havana and reached so successful an end to their labours. It would appear from this account that Gorgas was not at first convinced that the mosquito theory was true. But, once he was convinced by the work of the Commission, he lost no time in making use of the discovery and in instituting at Panama an entirely new type of disease control—in other words, anti-mosquito measures. This type of control was later to be extended and developed by others to include even such gigantic undertakings as the permanent nation-wide measures against *Aëdes aegypti* initiated in Brazil in 1932, dealing with an area of almost half a continent (Soper *et al.*, 1943).

There can be no doubt but that Gorgas, by his striking demonstration of the possibility of control of yellow fever by anti-mosquito measures, greatly hastened the adoption and development of such measures not only in America but as a necessary precautionary action in other parts of the world. It was, however, the discovery of the mechanism of infection by the Commission which enabled sanitation and administration to achieve these results.

The Yellow Fever Commission

The members of the Commission were Dr. Walter Reed, a surgeon in the United States Army and president; Dr. James Carroll; Dr. Jesse W. Lazear, the first of a number of martyrs to science who were to lose their lives in the investigation of yellow fever; and Dr. Agramonte, a name later very familiar in the literature of yellow fever. The centenary of Reed's birth is celebrated this year.

The Commission had originally been formed and proceeded to Cuba to investigate the claims that an organism isolated by Sanarelli was the cause of yellow fever. They remained to test out the mosquito theory. They were not the originators of the theory of mosquito transmission of yellow fever. This had been suggested before and had been strongly advocated at the time of the Commission's visit by Dr. Carlos J. Finlay, of Havana. Nor had Finlay been satisfied by mere hypothesis, for he had made a close study of the mosquito known to him then as *Culex mosquito* Desv., now *Aëdes aegypti*, pointing out that this was the domestic mosquito of Havana and bringing forward much evidence pointing to its probable role in the spread of yellow fever. He failed, however, to give the convincing proof of this, for in such experiments as he had made to transmit the disease he failed, not knowing of the necessity for an interval required for infection to develop in the vector.

So it fell to the skilfully conceived and perfectly carried out series of critical experiments by the Commission to bring fact in place of theory. Nor was this so simple as it may seem, for the more the work of the Commission is studied the more able, efficient, and skilled would their work appear to have been. They soon clearly and concisely showed that the *Leptospira* of Sanarelli was not the cause of yellow fever, their first task as a Commission, and that the mosquito did transmit the disease from man to man, that it did so only after a considerable interval, and that the disease was not contracted, as had always been thought, by contagion, fomites, or general filth. Moreover, Reed and Carroll showed early in the investigations that the cause of yellow fever was a filterable virus, the first time any human disease had been shown to be due to such an agent.

It is one of those curious happenings which sometimes occur in scientific research that, just when it seemed there was no further problem connected with yellow fever, a number of puzzling observations began to come into the picture that did not fit in with accepted ideas about the disease. Thus, while the general belief had been that yellow fever was entirely a New World disease, Boyce had early shown there was reason to believe that yellow fever had long been, and still was, present in West Africa.

Later observations not only confirmed Boyce's findings, but through the use of the "mouse test" showed that throughout a large part of tropical Africa, and extending far to the east of that continent, there existed in the indigenous population a considerable percentage of immunes, this discovery showing that yellow fever must quite recently have been present, if it was not still so, over large areas where its presence had never before been suspected. Work in America, too, had shown that all epidemics of yellow fever could not be ascribed to transmission by *Aëdes aegypti*, or even to infection derived from man, and that there existed a form of the disease characteristically contracted in the forest, which differed in its aetiology from that usual in urban epidemics, and which was not transmitted by *Aëdes aegypti* or due to man-derived infection, a form now known as jungle or forest yellow fever.

[1] *Physician to the World. The Life of General William C. Gorgas.* By John M. Gibson. (Pp. 316. £1 14s.) London: Cambridge University Press. 1950.

Virus Research

It was here that work in the laboratory on the virus came to the assistance of epidemiological work in the field. Ever since the discovery by Stokes, Bauer, and Hudson in 1928 that monkeys were susceptible to infection, and later that some other small mammals were so and could be used as laboratory animals in the study of the virus, there has been much work in this direction. It has given more information on the nature and behaviour of the virus and opened up many new lines of research in other directions. The "mouse test"—the intracerebral inoculation of white mice—has been a particularly valuable help to research. Not only has it been used, as already noted, in mapping the disease over large areas in the New and Old Worlds, but it has enabled us to test the power of different species of mosquitoes to retain or transmit the virus. In America this has shown that forest yellow fever is mainly contracted through mosquitoes of the genus *Haemogogus*, which receive infection from forest monkeys. Mosquitoes of this genus are strictly forest species breeding in tree holes. *Haemogogus* is a genus which does not occur in the Old World, and other species play this role in Africa, notably *Aëdes simpsoni* and *Aëdes africanus*, both of which species have been shown capable of transmitting the virus and have been found naturally infected.

A curious feature in the aetiology of forest yellow fever is that the vertical distribution of species of mosquito has been found to be important. Thus in the American forests it is especially when trees are felled, bringing down their high level mosquito fauna, that the chief danger of infection arises. In Africa it seems that *A. africanus* is the chief vector in maintaining the virus, receiving and transmitting infection in the high-level monkey community, but not ordinarily infecting man, who mainly receives infection from *A. simpsoni*, which frequents human neighbourhoods on the borders of the forest and acquires infection from monkeys infected by *A. africanus*.

These are not the only lines of investigation opened up by virus research. One important line of inquiry is directed to the production of a safe and effective vaccine which can be used on a large scale in human protection. At one time human immune serum was used to provide such protection, but naturally only on a very limited scale. Another method, now disused, was the simultaneous injection of mouse virus and immune human serum. There have been still other methods employed. Viruses, according to the strain or host used, may be mainly viscerotoxic, affecting chiefly the liver, etc., as in man and monkey, or neurotoxic, as in the mouse, the white mouse being susceptible only to intracerebral inoculation. The strains used for vaccine have been principally the Asibi strain of human source, which is mainly viscerotoxic, and the so-called French neurotropic strain. A vaccine, 17 D, giving modified action of both types has been prepared at the Yellow Fever Laboratory of the International Health Board from virus cultivated on the chick embryo (Theiler and Smith, 1937), of which 28 million doses have been issued for use in human protection.

Those who wish to learn more of these lines of research and much else about yellow-fever work should read *Yellow Fever*,[1] issued under the editorship-in-chief of George K. Strode. It gives the results of the work carried out on yellow fever over a period of more than 30 years by the Rockefeller Foundation and by other agencies with the support and co-operation of this body. This is in effect a monographic study of the whole subject of yellow fever, comprising a number of sections relating to different aspects of the disease by authorities who have themselves been recently engaged in and largely responsible for results in the work they write about. The book is attractively printed, very readable, and interesting throughout, and it will clearly be the chief reference book on yellow fever for a long time to come.

[1] *Yellow Fever*. Editor-in-chief, George K. Strode, M.D. (Pp. 710; 77 figures. £4 1s.) London: McGraw-Hill Publishing Company. 1951.

References

Boyce, R. (1910). *J. trop. Med. Hyg.*, **13**, 357.

Soper, F. L., Wilson, D. B., Lima, S., and Antunes, W. Sa. (1943). *The Organization of Permanent Nation-wide Anti-Aëdes aegypti Measures in Brazil*. Rockefeller Foundation, New York.

Theiler, M., and Smith, H. H. (1937). *J. exp. Med.*, **65**, 787.

HORMONES AND CARCINOGENESIS

Steroid Hormones and Tumors. Tumorigenic and Antitumorigenic Actions of Steroid Hormones and the Steroid Homeostasis. Experimental Aspects. By Alexander Lipschutz, M.D. (Pp. 310; 111 figures. £2 6s. 6d.) London: Baillière, Tindall and Cox. 1950.

The role played by steroid hormones in carcinogenesis is one of the most intriguing problems of experimental medicine, not only because cancer of the breast, uterus, and prostate gland are common sites of cancer in the body, and are organs normally under endocrine control, but because the growth and behaviour of tumours derived from these particular organs can under certain conditions be influenced by means of endocrine therapy. Although cancer of any of these organs cannot at present be permanently cured by this form of treatment, most encouraging results have been demonstrated clinically with the control of prostatic cancer in man by the application of anti-androgenic measures. The results obtained by hormonal treatment of the breast, and particularly of the uterus, have been less satisfactory, and for this reason Dr. Lipschutz's book is of exceptional interest. Many of the issues he raises are controversial, but he does attempt by his experiments with guinea-pigs to fill in certain gaps in our knowledge of the relationship of sex hormones to the genesis of uterine tumours. These tumours, and particularly carcinoma of the endometrium, are thought by many investigators to be related to hormonal disturbance, but whether uterine fibromyomas result from ovarian dysfunction is more debatable.

This volume consists of a series of original papers and observations by the author and his numerous colleagues, dating from 1936, some of which have never previously been published. Both clinicians and research workers will find it something more than just another of the detailed works of reference which so many modern textbooks tend to be.

The book is in three parts. The first is mainly on the induction by oestrogens of uterine fibromyomas and abdominal and thoracic fibroids in guinea-pigs. Controversy exists on whether these induced uterine lesions in the guinea pig are comparable histologically to those which occur spontaneously in human beings, but the fact that they can be induced by hormonal treatment is significant. It is also true that attempts to induce similar

uterine tumours regularly in animal species other than the guinea-pig, which is singularly susceptible, have been unsuccessful, but this should not detract from the value of these experimental findings. Part II is on what the author terms the "antifibromatogenic action" of different steroids, and particular attention is paid to the prevention of oestrogen-induced fibroids by administration of progesterone, desoxycorticosterone acetate, and testosterone propionate. The hypophysial-ovarian factors in the balance of steroids are discussed at some length in part III, which is perhaps the most controversial section of the book, since the author refuses to accept the current conception that oestogens can inhibit the gonadotrophic activity of the anterior pituitary. Dr. Lipschutz puts forward evidence based on his experiments that the gonadotrophic function of the anterior hypophysis is regulated by steroids.

Apart from the experimental work described in this volume, it also has its uses as a work of reference. It is well constructed, with clear headings to the several subsections, and the many photomicrographs are of good quality.

E. S. Horning.

ENCYCLOPAEDIA OF ANTIBIOTICS

Handbook of Antibiotics. By A. L. Baron. (Pp. 303. 52s.) New York: Reinhold Publishing Corporation. London: Chapman and Hall. 1950.

This book is a potted encyclopaedia of antibiotics, 143 of which are tersely described in alphabetical order. Successive sections in each account deal with discovery, methods of production, chemical constitution and other properties, action on bacteria (in the animal or patient as well as *in vitro*, if any such information is available), and pharmacology. A "bibliography" accompanies each item, but when, as in connexion, for instance, with herquein, inolomin, and irpexin, this consists of a single publication, this heading and the stock phrase "first described by" (when "first" may possibly mean "only" for all time) seem perhaps unduly flattering.

It is almost true to say of some of the better-known antibiotics that the space allotted to them varies in inverse proportion to their therapeutic utility. Thus the accounts of penicillin and streptomycin are deliberately made short, because if adequate they would "completely unbalance" the book. They occupy two and three pages respectively, whereas neighbouring accounts of polymyxin and streptothricin get nine and eight. The description of the newer antibiotics in therapeutic use are remarkably good in view of the publication date, but 25 of the 26 items in the bibliography on terramycin are from a single number of one journal, of which the author seems to have had advance proofs, and the account of the clinical use of this drug is incorrect in stating that it is ineffective in staphylococcal infections. Clinical information (of which there is none in connexion with most of the substances described) is not a leading feature, and there is sometimes no hint of what has been hoped of a new antibiotic. No reader would suppose, for instance, that clitocybine had been hailed as a remedy for tuberculosis, or that it was to the treatment of this disease that the discoverer of neomycin had pinned his faith in the drug.

When all this has been said, and when it is appreciated that most clinicians will not find much here to help them, the fact remains that this book is a prolific source of readily accessible information of many kinds, indispensable to an investigator in this field, and invaluable to anyone whose interest in antibiotics extends beyond their clinical use.

L. P. Garrod.

MARRIAGE OR PROFESSION

The Encircled Heart. By Josephine Elder. (Pp. 271. 8s. 6d.) London: Lutterworth Press. 1951.

Contrary to what may be the first thought of the reader of the title of this book, it is not a treatise on a hitherto unchristened form of cardiac disease. It is a novel by a practising doctor writing under a pseudonym. Its chief characters are doctors and most of the rest figure as patients. Its main theme is a problem that has been faced by many doctors, and other professional men and women, with varying success: Is it wise for a professional person to marry one who has a promising professional career of his or her own and is unwilling to give it up?

The heroine of this book is a busy general practitioner and loves her work. Until she meets the man involved (who is a university lecturer on education) she believes she has found in her practice a completely satisfying way of life. They marry, and at first all is bliss, until the husband finds that a busy woman doctor cannot give him the time and attention he thinks a man should expect from his wife. There follows a period of strain, which is temporarily ended when they have two children and the practice is—reluctantly—given up. Later the war takes the husband off to India for some years and the wife jumps at the chance to join the hard-driven local general practitioner. I must not give away the complications which follow, but all ends more or less happily, though I thought the loose ends were not tied up very neatly.

The author is very successful in describing the trials and pleasures of family practice. Her general practitioner may be slightly romanticized, but she has the right conception of what constitutes the good family doctor. I thoroughly enjoyed the book, so can cordially recommend it to doctors—and patients.

Alfred Cox.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

The Formation of Adrenaline in the Body. By Professor J. H. Burn, M.A., M.D., F.R.S. Sir Jesse Boot Foundation Lecture, 1950–1. (Pp. 19. 1s. 6d.) Nottingham: The University. 1951.

Der Naturforscher Goethe. By the Rudolph Virchow Medical Society. (Pp. 77. No price.) New York: Rudolph Virchow Medical Society. 1949.

Curriculum Vitae e Indice de las Publicaciones Cientificas. By E. Ingber. (Pp. 48 No price.) Buenos Aires. 1951.

Über den Blutfarbstoffwechsel gesunder Säuglinge und Kinder. By W. Künzer. (Pp 86. 11 Swiss francs.) Basle: S. Karger. 1951.

Die Anatomischen Schriften. Edited by Dr R. Kapferer. (Pp. 55. $3.50.) Stuttgart: Marquardt 1951.

Allgemeinpathologische Schriftenreihe. Edited by Professor G. Ricker and Professor H. H. Kalbfleisch. Vol. 8. (Pp. 125. No price.) Stuttgart: Marquardt. 1951.

Die Durchblutungsstörungen der Gliedmassen. By Dr. W. Block. (Pp. 298. M. 38.) Berlin: Walter de Gruyter. 1951.

BRITISH MEDICAL JOURNAL

LONDON

SATURDAY OCTOBER 6 1951

BACTERIOPHAGE

Since its discovery some 35 years ago, bacteriophage has been widely studied as a therapeutic agent, as a means of typing bacteria, and, because of the ease with which it can be manipulated, as a "model" virus.

Its potential therapeutic properties have been a constant lure, and many attempts have been made to reproduce *in vivo* the dramatic bacterial lysis which it causes *in vitro*. At first sight it would appear that phage ought to provide an ideal means of overcoming bacterial infection. But, just as in laboratory experiments a resurgence of bacteria—frequently in the form of resistant mutants—occurs when incubation is carried beyond the stage of lysis, so in the living body a state of balance between bacterium and phage is soon reached, in which bacterial multiplication takes place freely. It is true that in a few abnormal and artificial infections in laboratory animals an apparent cure has been achieved by the action of phage—as, for example, in dysentery infections of developing chick embryos or in parenteral dysentery infections in mice. In natural infections, however, such as *Salmonella pullorum* in chicks and *S. typhi-murium* in mice, no significant benefit has resulted from its use.

In certain bacterial infections of man some investigators have claimed that the administration of phage will arrest development and hasten cure, but the supporting evidence is unconvincing and has not been confirmed in controlled trials. Thus, in localized pyogenic infections a few reports of good results are counterbalanced by more careful observations where no improvement was noted. Perhaps the most insistent claims have been made for the benefits of phage treatment in bacillary dysentery, but even here the majority of workers have been unable to repeat such findings. The position as regards typhoid fever is interesting. The intravenous administration of small quantities of Vi phage produces an immediate reaction which is succeeded by a crisis and rapid convalescence. However, it must be remembered that the "bacteriophage" which is injected also contains protein from lysed bacteria, and the response which occurs may well result from specific protein shock.

Most observers agree that, up to date, phage has failed as a therapeutic agent. If, for the building up of a concentration capable of giving significant bacteriolysis, reliance is placed on the multiplication of phage in the patient's body at the expense of the infecting bacteria, it seems unlikely that success will ever be achieved. It is possible, however, that, by the administration of sufficient purified phage to produce a high concentration immediately, better results would be obtained, but many difficulties will have to be overcome before a trial of this method can be made.

An important and practical use has been made of phage in typing certain species of bacteria—notably the enteric group organisms. This procedure dates from the discovery of a phage showing activity only against strains of *Salmonella typhi* endowed with Vi antigen.[1] This phage can be conditioned so that it picks out varieties or types of the organism in which this antigen shows minor shades of difference. Such differences are permanent hereditary characters in the bacterium, and it is therefore possible to use them to divide up the species into types, of which some 29 are now recognized. The same method has subsequently been applied to *S. paratyphi* B, of which 10 types and subtypes are recognized, and to *S. typhi-murium*,[2] and may also prove to be applicable to *S. paratyphi* A.[3] Another method has been devised for typing staphylococci by means of phages which are related to the O antigens of these organisms.[4] These O phages are not specific for one type of organism as are the conditioned Vi phages, but give varying reactions with different strains. With a selected series of phages a pattern of positives and negatives is obtained from which the type of the staphylococcus can be identified. This method is less precise than the previous one, but nevertheless is useful in "matching" strains. The same technique has been applied with varying degrees of success to other kinds of bacteria. Yet another method for typing *S. typhi-murium* has lately been described, based on the

1 Craigie, J., and Yen, C. H., *Canad. J. publ. Hlth*, 1938, **29**, 448.
2 Felix, A., and Callow, B. R., *British Medical Journal*, 1943, **2**, 127.
3 Felix, A., *Brit. med. Bull.*, 1951, **7**, 153.
4 Wilson, G. S., and Atkinson, J. D., *Lancet*, 1945, **1**, 647.
5 Boyd, J. S. K., *J. Path. Bact.*, 1950, **62**, 501.
6 Felix, A., and Anderson, E. R., *Nature, Lond.*, 1951, **167**, 603.
7 Nicolle, P., Hamon, Y., and Edlinger, E., *Ann. Inst. Pasteur*, 1951, **80**, 479.
8 Hamon, Y., and Nicolle, P., ibid., 1951, **80**, 496.
9 Lwoff, A., and Gutmann, A., ibid., 1950, **78**, 711.
10 Burnet, F. M., and Lush, D., *Aust. J. exp. Biol. med. Sci.*, 1936, **14**, 27.

identification of the various strains of symbiotic or latent phage which are to be found in most cultures of this organism.[5] It is of interest to note that some recent work from other sources[6-8] shows that certain of the *Salmonella typhi* and *S. paratyphi* B types owe their characters to the latent phage they carry : it is probable that this aspect of the subject will now receive increasing attention. All these methods have the same practical application. By dividing bacterial species into types or races they enable the epidemiologist to trace the source and spread of outbreaks of infection with much greater precision than would otherwise be possible.

While the name " bacteriophage," originally coined by d'Herelle, is still in general use, it has long been recognized that phages are in fact bacterial viruses and have much in common with the viruses which affect plants and animals. Because of this relationship, and in the hope that observations made on bacterial viruses would point the way to the solution of some of the problems of virus disease, much research has been devoted to the elucidation of the several factors which influence the development of phage. Most of this research has been carried out on lytic phages—i.e., those which, in multiplying, destroy the host-bacterium—in particular on the T series of coliphages, which were selected for exhaustive investigation by a group of workers in the United States. A mass of information, too extensive to detail, has been accumulated concerning the complex physical and chemical aspects of the processes of adsorption of phage to bacterium, of penetration, and of subsequent multiplication of the virus in the bacterium. It has been found that multiplication does not take place by repeated binary fission, although at one time evidence from electron photomicrographs seemed to indicate that this was so. Under standard conditions there is a relatively constant interval between penetration of the bacterium by the phage and the final rupture of the organism which signals the liberation of a crop of phage particles. During the greater part of this latent period it is impossible to recover active phage from the infected organism. There is considerable evidence to support the theory that after entering the bacterium the phage loses its identity and assumes the character of a dominant gene or genes, which divert the enzymes of the host-bacterium from their normal functions to the fabrication of the particular components of the phage. When, towards the end of the latent period, enough of such material has accumulated, some critical stimulus causes it to be abruptly organized into discrete and mature phage particles. The theory of dispersal (in which the virus occurs in a state which some workers call the " soluble phase ") receives confirmation from the remarkable observation that when a single bacterium is infected by two related phages the resulting crop contains not only replicas of the original types but also hybrids having some of the characters of both, suggesting a re-combination of the dispersed genetic units in varying patterns. This finding is of much interest to geneticists and may explain the changes in antigenic structure which occur in certain viruses —such as, for example, the influenza virus.

By focusing attention on these lytic phages there has been a curious neglect of the problems associated with the symbiotic or latent phages which occur in cultures of the so-called lysogenic strains of bacteria. In the last few years, however, interest in this subject has revived. Some recent experiments with microcultures of lysogenic bacteria[9]—cultures from single bacteria in minute droplets of medium—have shown that many apparently normal divisions of the bacterium can occur without lysis, although each daughter-bacterium contains the latent phage. Ultimately, however, one of the bacteria ruptures. Before this occurs there is no free phage in the culture: afterwards there is. The authors of this work attribute the occurrence of lysis to the emergence of a mutant bacterium which is sensitive to the latent or immature phage and permits it to develop to maturity. An alternative explanation is that, as the result of mutation of the phage, an otherwise normal bacterium is infected with a lytic and not a symbiotic phage particle, following which the familiar cycle of phage multiplication and bacterial lysis follows its inexorable course.

Some years ago an account was given of the recovery from a lysogenic staphylococcus of a symbiotic phage which produced permanently lytic variants.[10] A similar observation has recently been made in relation to certain phages of *S. typhimurium*.[5] It has been suggested that all the familiar lytic phages (among them the typing phages and the T series of coliphages) take origin as mutants of symbiotic phages, and that in natural surroundings the better-established symbiotic types are the continuing source of these more vulnerable lytic strains, which otherwise can survive only by making recurring contacts with a series of sensitive (and foredoomed) host bacteria. This conception of variation from the innocuous symbiotic phase to the destructive (virulent)

lytic phase has implications of great importance for both bacterial and animal viruses and indicates a new line of approach to many of the problems of virus disease.

CARCINOMA OF THE BRONCHUS

It is generally accepted that the treatment of patients with bronchial carcinoma by means of pneumonectomy offers the best hope of long survival. Mason[1] recorded four patients surviving out of 33 who were operated on between four and a half and seven years before the time of his survey. He saw 1,000 cases in his clinics between 1933 and 1948, and found it possible to carry out pneumonectomy in 202 of these. It is interesting that, although the number of patients with this disease referred to him rose during the 15 years from a few to approximately 200 a year, he noted that the percentage with operable growths had fallen. Moreover, in a recent paper by Brooks, Davidson, Price Thomas, Robson, and Smithers[2] it is estimated that, of the 9,000 persons dying each year in England and Wales of bronchial carcinoma, fewer than 200 undergo pneumonectomy. Watson and Smith[3] have recently reported that a type of growth they classify as "terminal bronchiolar or alveolar cell cancer of the lung" may be more amenable to surgical excision than other forms, though radical surgery was possible in only 14 of their 33 patients.

The paper by Brooks and his colleagues is a survey of the work of the joint consultation clinic for neoplastic diseases which was established in 1944 by members of the staffs of the Brompton Hospital and the Royal Cancer Hospital in co-operation. Much of the importance of this valuable and interesting report lies in the fact that it is concerned in part with assessing non-surgical methods of treating bronchial carcinoma. Between 1944 and 1948 (both years inclusive) 502 patients with carcinoma of the bronchus were seen at the joint clinic. In all cases the diagnosis was accepted only after careful consideration, and when a patient survived one year or more from his first visit the evidence was critically reviewed. There was histological confirmation of the diagnosis in 306 patients, and in 196 it was based on good clinical grounds. The report makes clear that this group of patients is a highly selected one. During the period of the survey there were a further 440 patients who were seen at the Brompton Hospital and diagnosed as having bronchial carcinoma but not referred to the clinic: these were mainly patients who were thought to be so ill when first seen as to be unsuitable for reference to the clinic, and also some who could be treated surgically. Although in general patients found suitable for operation were not sent to the clinic, a small number of those who were referred were treated by surgery or combinations of surgery and other methods.

Chemotherapy and radiotherapy were the two non-surgical methods of treatment which the authors discuss. Seventy-five patients were treated with chemotherapeutic agents. Of these, 54 had chemotherapy alone—seven being given urethane, four dienoestrol, and 43 chlorethylamine. The authors comment that they saw no benefit from urethane or dienoestrol. Improvement was observed in some patients treated with the chlorethylamines, but in general the discomfort of this treatment, which usually causes repeated vomiting, outweighed its temporary benefits. In the remainder of this group of 75 patients chemotherapy was combined with *x*-ray therapy or with surgery.

The patients who received *x*-ray treatment were divided into two groups: those who received radical courses, and those who had palliative treatment for the relief of symptoms. In most cases the distinction between these groups is clear, but sometimes treatment which was begun with the aim of relieving symptoms only was persisted with, and these patients were therefore included in the radical group, though their total dose of *x* rays may have been comparatively small. One hundred and seventy-six patients received palliative treatment; of these one was alive 21 months after treatment; four had been lost sight of, and the remaining 171 were dead, with an average survival of 5–6 months after treatment. So far as symptomatic improvement was concerned, it was found that relief of haemoptysis was usual, though the symptom sometimes returned; cough was nearly always lessened and sometimes completely banished; and superior vena caval obstruction was often, and dyspnoea sometimes, relieved. Pain from secondary deposits in bone could often be alleviated, but patients with pain in the chest, particularly that due to direct extension of the growth to the pleura and ribs, were benefited less often and sometimes not at all. This method of treatment was of no benefit to those with pleural effusions. Patients with much sepsis in the affected lung as a result of infection beyond the bronchial tumour usually felt worse after irradiation, though penicillin and postural drainage may help to lessen this disadvantage when the bronchus is not completely blocked. Those in poor general condition

[1] *Lancet*, 1949, **2**, 587.
[2] *Thorax*, 1951, **6**, 1.
[3] *J. Amer. med. Ass.*, 1951, **147**, 7.

rarely get more than very temporary relief, which the authors feel is seldom worth the effort made by the patient or the radiotherapy department.

Radical *x*-ray treatment, which is an attempt to destroy the tumour, was given to 129 patients. Almost all of these were regarded as having inoperable growths, but in many cases the treatment prolonged life: 30 patients were alive at the time of the survey—that is, after at least a year from treatment—and of those who had died the average period of survival was 10 months. At the present time it cannot be doubted that relief of symptoms is the best that can be offered to most sufferers from this increasing and predominantly male disease. As Brooks and his colleagues claim, *x*-ray therapy offers the only means of symptomatic relief in the majority of patients.

AFTER PNEUMONECTOMY

What happens to the space left after a pneumonectomy was discussed at the recent meeting in Paris of the International Society of Surgery. The opening speaker described how the normal process is for the space to fill up with blood and with serous exudate; this progressively organizes to form a solid fibrothorax and serves as a natural filling. In most cases this is entirely satisfactory, and with an experience of more than 200 pneumonectomies over a period of fifteen years he had found this natural healing to be the best in almost all cases; several patients had now been followed for nearly fifteen years and many for more than ten years. The possibility of overdistension emphysema of the remaining lung is a matter of concern; if it occurs it may cause reactivation of disease (for example, in tuberculosis) and also result in impaired function. Overdistension is seen under three conditions. In children the power of compensation is so great that the remaining lung may fill almost the whole chest, but this does not seem to cause loss of function unless the lung is already abnormal. In older people with bronchitis and emphysema the previously damaged lung may become much overdistended, with increasing emphysema. The third condition favouring overdistension is aspiration and air replacement of the natural exudate. Although air refills maintain the central position of the mediastinum for a time, eventually intense pleural fibrosis and contracture lead to extreme examples of the very conditions that it has been sought to avoid—overdistension and loss of function. Unless the fluid accumulates so as to cause mechanical embarrassment it should not be removed, but should be left to organize. Recent papers on liquefaction and removal of this natural clot with streptokinase ignore the importance of conserving the clot.

Some surgeons, realizing that refills cannot be maintained indefinitely, have suggested that the pneumothorax be replaced by an oleothorax or by insertion of an artificial plastic filling. Experiences with the disastrous later results of oleothorax in the management of tuberculosis give little reason for confidence in its use after pneumonectomy. As yet little is known of the reaction of the body to a filling prepared from plastics, but from the use of other foreign bodies in surgery it is far from certain that even the new plastics will provide the safe answer: certainly it is difficult to feel confident that the use of a plastic filling in the chest of a young patient will not in later years be followed by very serious trouble. The filling may not even prevent overdistension, but can be squeezed smaller, like a sponge, before the powerful secondary fibrosis. In the discussion at the Paris meeting the speakers who described their methods of filling the cavity had been able to follow their patients for only a short period. One speaker reported his experiences with injection of blood into the space to augment the natural filling. This caused severe reactions, probably because the blood came from a donor. If this method is used—and it is unquestionably the most logical—the patient's own blood should be given.

Thoracoplasty has been widely credited and somewhat unreservedly accepted as being able to prevent, check, or correct overdistension of the remaining lung. But the problem is not so easy as this, for it is clear that satisfaction with its results is not always justified. Cournand,[1] in an earlier study of the impaired function in the remaining lung after pneumonectomy, suggested that thoracoplasty could be used to prevent this, but in a later and fuller report[2] he states that thoracoplasty actually reduces the function of the remaining lung, chiefly due to scoliosis. Gaensler and Strieder,[3] in a recent study of the effects of thoracoplasty done early (less than two months) and late, came to the same conclusion. Early thoracoplasty actually overcorrects the distension and impairs function. Late thoracoplasty does exactly the reverse of what is aimed at: it fails to correct the overdistension and inflicts further loss of function. It is high time that the drawbacks of thoracoplasty were more widely known, for many patients are still being submitted to thoracoplasty after pneumonectomy almost as a routine—in many cases quite unnecessarily and often actually harmfully. This is particularly so after pneumonectomy for tuberculosis, although thoracoplasty must inevitably retain a valuable place in the management of the residual space in order to lessen the chances of pleural infection by aiding early fusion of the walls and to check reactivation of contralateral disease; for both these purposes it should be done within three to six weeks after operation. One of the grave objections to thoracoplasty after pneumonectomy is that it inflicts another severe operation or series of operations on a patient who has already had a serious one. For this reason alone it should not be done as a mere routine.

After pneumonectomy for carcinoma thoracoplasty should scarcely ever be considered before one year because of the considerable chance of recurrence within that period. To inflict a second severe operation when

[1] *Ann. Surg.*, 1942, **116**, 532.
[2] *J. thorac. Surg.*, 1950, **19**, 80.
[3] Ibid., 1951, **22**, 1.

recurrence is at all possible seems quite unjustifiable. The only application that thoracoplasty should have in conjunction with pneumonectomy for carcinoma is in space infection, when it may help obliteration. Space infection is the greatest problem after pneumonectomy, especially if, as is usually the case, it is associated with a bronchial fistula. In some cases aspiration and injection of antibiotics may bring about sterilization. In others external drainage is needed—always if a fistula is present. After a period of drainage, if no fistula is present or if one has healed, sound and permanent healing often follows removal of the drainage tube: the opening speaker at the Paris meeting quoted examples of patients who had remained well, with the wound healed, for over ten years. If a bronchial fistula persists, removal of the tube is useless. It remains then to recommend either retaining the tube permanently, which is often the best advice to an elderly unfit patient, or to perform a thoracoplasty. Even a radical thoracoplasty may fail to achieve healing, although it will of course materially reduce the size of the infected space and the amount of discharge. Complete healing may then be possible only by a further series of open, musculoplastic operations, which are often not justified unless the patient is young and the original disease was not malignant.

TUBERCULOSIS IN SCHOOL

Epidemics of tuberculosis are rarely reported, probably rarely discovered. The outbreak reported this week by Drs. Bevan, Bray, and Hanly (p. 828) leads one to believe that it is the detection of outbreaks which is rare, and not their occurrence, for there is nothing remarkable in the character of the one they describe except its detection. A paediatrician saw five cases of primary tuberculosis from one area and informed the county medical officer of health; it was found that all five children attended the same school. The children at the school were tuberculin-tested; those positive were radiographed. A high percentage of positives was found in one class; the teacher in charge of this class (Standard III) had "laryngitis" two months previously, returned to work, but at the time of the investigation was again away with "haemoptysis" and was found to have respiratory tuberculosis. Tuberculin tests were repeated in November. At the completion of the investigation it was found that 75% of the pupils in Standard III were tuberculin positive, compared with less than 40% in other forms. *X*-ray evidence of tuberculosis was found in 6 of the 28 pupils in this form, and also in 4 of 49 children in the infant class, who had been under the charge of the same teacher for five days during the temporary absence of their class teacher.

The authors are to be congratulated on their prompt action in this outbreak. They demonstrate that, despite the apparent division of responsibilities in tuberculosis under the National Health Service, there need be no obstacle to prompt and close co-operation between the authorities involved. In this case action was taken jointly by the paediatric, public health, chest clinic, and general-practitioner services; there is little reason, except the unreason of personalities involved, why such joint action should not be seen in all fields of tuberculosis work.

The other problem raised is that of tuberculosis control in adults working in close contact with children and young people. The outbreak reported did not produce any serious case of tuberculosis, and in fact most of the cases would normally have been undiagnosed; but this can be considered as fortuitous, for any one of them might have developed a much more severe form of the disease. Many countries have already accepted the principle of compulsory periodic examinations for school-teachers and other adults working with groups of children. Although periodic examinations would not provide a complete guarantee, they must reduce the risks of the occurrence of such outbreaks. It may justifiably be argued that compulsory examination may be applied only if prompt and adequate treatment can be guaranteed when disease is found, and also adequate economic provision during absence from work for treatment. This is a question which must be resolved, and should be taken up by full and frank discussion between the Ministry of Health and the organizations of teachers and other workers concerned.

THE "PRACTITIONER"

This week the *Practitioner* celebrated the publication of its thousandth number. This is a good round figure and affords an occasion for congratulating those who are continuing the tradition of over eighty years of providing for the medical profession a monthly journal which stresses the practical side of the art and science of medicine. The thousandth issue follows the custom adopted by the *Practitioner* at this time of the year of reviewing advances in treatment in the past year. As an introduction to the thirteen articles on advances in various branches of medicine there are three of a more general nature. The first, by Sir Henry Dale, surveys the changing face of medicine since 1868, the date of the first appearance of the *Practitioner*; the second, by Sir Henry Bashford, is on the social background of medicine, and the third, by Dr. W. N. Pickles, on trends of general practice over the past hundred years as noted in retrospect in a Yorkshire dale. The contributors to the survey of advances during the current year include three from the U.S.A., one of whom writes on surgery, another on allergy, and the third on endocrinology. A fourth article from across the Atlantic is devoted to the use of cortisone in rheumatic diseases, and, as Dr. Freyberg points out, much more information is needed before we can use cortisone in general clinical work. He stresses that the many undesired physiological effects markedly limit the clinical usefulness of cortisone—a warning note that will not be lost upon those many readers who look to the *Practitioner* for guidance in clinical medicine.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

INTERNAL DERANGEMENTS OF THE KNEE-JOINT

BY

I. S. SMILLIE, Ch.M., F.R.C.S.Ed., F.R.F.P.S.

Lecturer in Orthopaedics, University of St. Andrews

The knee is the largest and also the most vulnerable joint in the body. In general, it is hinge-like in character, depending for stability primarily on the active control of the powerful quadriceps group of muscles, and secondarily on the passive control of the ligaments. The latter structures determine the direction in which muscle action is transmitted to the moving surfaces and achieve through their sensory nerve fibres the co-operation essential to protection from injury. The arrangement of the muscles about the joint is such, however, that when the knee is extended, or almost extended, the leverage exerted is relatively small and the protective power limited; nor is there any position within the range of motion in which muscle action has any considerable control over lateral bending or rotation.

That the knee can attain any degree of stability in extension, and indeed is not even more vulnerable, is due to the all-important quadriceps and to the complex action which differentiates the joint from a simple hinge —namely, the "screw-home" movement. This is the mechanism whereby, at the completion of extension, the tibia rotates laterally by the indirect action of the quadriceps, guided in its course by the anterior cruciate ligament and the form of the articular surfaces. The screw-home movement is an important feature of the knee-joint mechanism not only because it determines the stability of the joint in extension but because disorders of its complex action are responsible for most of the common internal derangements of the knee.

Importance of the Quadriceps and Ability to Attain Complete Extension

There are two related factors which, above all others, influence the rapidity of recovery of function following disease or injury. Neither appears to be completely understood; both are still neglected in treatment.

Volume and Tone of the Quadriceps.—When the knee-joint is affected by disease, accident, or operation reflex inhibition of the quadriceps takes place. Muscle wasting is extremely rapid, and the volume is reduced at a much greater rate than it can ever be regained by the most conscientious exercise. Active treatment is therefore a matter of urgency if the period of disability is to be reduced to a minimum. Treatment consists in non-weight-bearing exercises such as straight leg raising and quadriceps drill (quadriceps-setting) which do not entail movement of the joint and cannot therefore produce aggravation of the disease or injury. There are few exceptions to the rule that five minutes of exercise in every hour throughout the waking day should be observed throughout the period of recumbency and thereafter until the muscle bears comparison with the normal side. No passive therapeutic measure has been discovered which is a substitute for active exercise. The patient, the physiotherapist, and the practitioner should not be under any illusion that the time-honoured use of heat and massage does anything more than stimulate intramuscular circulation before treatment: treatment consists in exercise.

Ability to Attain Complete Extension.—The vastus medialis (vastus internus) component of the quadriceps is selective in action and comes into force in producing the final 10 to 15 degrees of extension, although it is used throughout the whole range in overcoming marked resistance. In spite of the apparent insignificance of such an operational range, the vastus medialis is by far the most important component of the quadriceps apparatus. These final few degrees of extension, including as they do the screw-home movement, are the most vital in the whole range. Witness the marked selective wasting which is present when for one reason or another full extension is permanently lost. Those elusive final 10 degrees are always something to strive for in the recovering joint, for without them redevelopment of the medialis component is impossible and perfection of function unattainable. In this respect the acutely swollen knee should not be "made comfortable" flexed over a pillow. If an effusion is so great as to demand the flexed position, it is great enough to demand aspiration.

Diagnosis

The term "internal derangement of the knee-joint" is commonly applied to those intra- and extra-articular affections, most often of traumatic origin, which are the result of lesions of the menisci (semilunar cartilages) —rupture of the cruciate, medial, and lateral ligaments, recurrent subluxation of the patella, loose bodies, etc. The term is thus no more than a statement that there is something wrong with the joint. It is not without significance that the abbreviation "I.D.K.," which so often adorns case records, also stands for "I don't know."

In diagnosing an internal derangement of the knee-joint it may be necessary to listen to the patient's story for only a few moments to appreciate, for example, that he is suffering from a complete longitudinal (bucket-handle) tear of the medial meniscus. On the other hand, a large proportion of cases present a complicated problem solved only by balancing every shred of evidence available. In this respect it is hardly possible to overstress the importance of the history. In many cases of long standing there may be no definite physical sign on which a diagnosis can be based.

The approach to the problem can usefully be illustrated by considering some common features in relation to diagnosis.

Mechanism of Injury.—The menisci are torn in a rotation mechanism when the productive force is seldom more than the patient's superimposed body weight. The common sprains of the upper femoral attachment of the medial ligament are similarly produced. Major lesions of the ligaments, involving complete solution of continuity, usually occur as a result of external violence, as for example in a motor-cycle accident or from a fellow football-player falling against the lateral side of the extended knee.

Immediate Incapacity.—It is seldom possible for a player to complete a game of football with a torn meniscus, even if reduction has been achieved by one of his colleagues; he usually tries, but he generally fails. In contradistinction,

a footballer sustaining an injury such as a direct contusion or a sprain of the upper femoral attachment of the medial ligament, although he may suffer severe pain at the time, usually manages to complete the game.

Locking.—The patient's statement that the knee "locked" should never be accepted until he has explained what he means by locking and demonstrated the position in which the knee was fixed. The locking produced by a bucket-handle tear of a meniscus usually takes place at a point 10 to 40 degrees short of full extension. It is sudden and definite in character and the unlocking equally sudden and even more dramatic. When true locking is associated with a history otherwise suggestive, it is almost pathognomonic of a torn meniscus and must be regarded as one of the most important of the diagnostic points available; but it must be emphasized that not more than half of the cases in which the meniscus is proved at operation to be damaged exhibit this particular symptom. The locking of a meniscus, at least on the first occasion, occurs while doing something abnormally active like coal-mining or playing football; the locking of a loose body or habitual subluxation of the patella is transitory and occurs during an everyday action like walking down stairs.

Giving-way.—While there are several causes for the complaint that the joint "gives-way" or "lets me down," such as an old rupture of the anterior cruciate ligament, quadriceps insufficiency, or a permanently displaced meniscus producing loss of full extension and consequently of the screw-home movement, by far the most common underlying lesion is a longitudinal tear of the posterior segment of a meniscus. If such a tear is confined to the posterior segment, insecurity may be the only serious symptom present. Some idea of the nature of the underlying lesion may be deduced from the patient's account of the incidents. Giving-way due to an old rupture of the anterior cruciate ligament, quadriceps insufficiency, or loss of full extension occurs on descending stairs or jumping from a height. That due to a torn meniscus takes place as a result of a rotatory movement such as turning round suddenly, stepping on a small stone, or walking on uneven ground, and is accompanied by the sensation of something loose in the joint.

Effusion.—The reaction of the synovial membrane to irritation is effusion, whether the irritation takes the form of direct contusion, minor sprain, or the stretching of the peripheral synovial attachment of a meniscus as occurs in a bucket-handle tear. The presence of effusion alone is, of course, no indication that a meniscus has been injured, but it is of assistance to remember that a meniscus is seldom, if ever, torn in the absence of effusion at the original accident. It is important to differentiate a simple traumatic synovitis from a traumatic haemarthrosis, not only because of the desirability of aspiration in haemarthrosis but because of the existence of concomitant lesions, in the form of serious ligamentous injury, which haemorrhage into the joint implies. In this matter the history may be of assistance: in acute traumatic synovitis there is usually an interval of about six hours between the injury and the appearance of swelling, whereas in traumatic haemarthrosis the swelling occurs within half an hour.

Pain and Tenderness.—If the patient can locate accurately the site of the pain it is undoubtedly of assistance in deciding upon the source of the lesion. The most constant and reliable region of localized tenderness in injuries of the medial meniscus is the collateral ligament at the level of the joint line. This clinical finding is not well known; in fact its presence is sometimes given as a reason for eliminating the possibility of a meniscus lesion in favour of a diagnosis of sprain of the ligament. The tenderness which is found in the common sprain of the medial ligament, existing as an isolated lesion, is localized in the great majority of cases to the upper femoral attachment.

Quadriceps Wasting.—Perfect muscles seldom control imperfect joints. Some wasting of the quadriceps is the accompaniment of every internal derangement of the knee; but, because of the rapid loss of volume which may follow even a short period of complete functional inactivity, the degree of wasting is not of necessity any indication of the gravity of the underlying lesion. The importance of the vastus medialis has been stressed. Thus it is that the earliest manifestations of wasting are seen in this component of the quadriceps apparatus. It is for the same reason that a better estimation of loss of volume and tone may be obtained by inspection and palpation than by the use of a tape measure. Many thighs are clothed with a thick layer of subcutaneous fat. A degree of flattening which cannot be measured can be appreciated by the eye.

Lesions of the Menisci

In Britain most meniscus injuries occur on the football field or in the coal-mine. On the football field the tibia is fixed by the studs of the boot, and thus the situation may arise in which forced extension may occur in the absence of lateral rotation of the tibia—the screw-home movement—or forced flexion in the absence of medial rotation of the tibia. In the cramped conditions of the narrow seams of a coal-mine rotation of the tibia is rigidly controlled by contact of the medial or lateral side of the foot with the floor. In such circumstances flexion and extension may not be accompanied by the appropriate rotatory movement of the tibia on the femur or of the femur on the tibia.

When the joint is suddenly extended, in the absence of synchronous lateral rotation of the tibia, the meniscus is caught in an abnormal position and is trapped against the head of the tibia, resulting in a longitudinal tear. If the tear involves only the posterior third the entire meniscus springs back into the normal position and the joint does not lock. If the tear extends forwards beyond the plane of the ligaments into the anterior segment the femoral condyle traps the meniscus against the tibia at the extreme anterior limit of the tear, the centrally displaced fragment cannot regain its normal position, and the joint locks.

The characteristic clinical feature of locking is the inability to extend the joint. What is less well recognized, but more important, is the block to lateral rotation of the tibia, and thus to the screw-home movement, which displacement of the medial meniscus entails. The significance of this statement in relation to the future function of the joint will be evident later.

The treatment of the torn meniscus is determined by two factors: (1) the meniscus is a structure devoid of blood supply—tears of the substance of the fibrocartilage cannot heal; and (2) weight-bearing activity in the presence of a permanently displaced bucket-handle tear, or a tear apt otherwise to produce locking or giving-way incidents, leads inevitably to rupture of the anterior cruciate ligament, deterioration of the joint, and eventually to osteoarthritis.

Injuries of the menisci are encountered in one of three forms:

(1) *The joint is locked.* In these circumstances the diagnosis is seldom open to question whether the locking occurred at the original accident or at a subsequent incident. The locked joint should be reduced to eliminate pain and discomfort, to prevent further damage, and to enable arrangements to be made for the rational treatment of a lesion which does not heal—namely, excision of the entire fibrocartilage. The action to be taken after reduction or in the presence of other indisputable evidence of a torn meniscus is: (*a*) application of a compression bandage; (*b*) rest, preferably in bed—weight-bearing is undesirable; (*c*) the immediate institution of quadriceps exercises; (*d*) removal of the compression bandage several times daily

for knee-flexion exercises; and (*e*) operation as soon as the preparation of the skin, the availability of a hospital bed, and the personal views of the orthopaedic surgeon will permit.

(2) *It is an acute injury, presenting difficulties of diagnosis, in which a meniscus lesion is suspected but cannot be proved.* There are few more difficult problems than determining the exact nature of the lesion in the acute injury with no history of a previous accident. The difficulty arises in the case seen for the first time at any period varying from a few hours to two to three weeks after the accident and showing little more than effusion accompanied by vague tenderness localized to the joint line. In this common problem, where a clinical and a radiological examination show no lesion other than a potential but unproved meniscus injury, the attitude to be adopted is one of expectancy. The case should be regarded as a traumatic synovitis and treated with compression in the form of alternating layers of wool and domette bandage, together with quadriceps exercises. No attempt should be made to safeguard the reputation of the practitioner by forbidding the return to athletic activities. When the volume and tone of the quadriceps have recovered, the resumption of football should be encouraged rather than discouraged. It is only in this way that the joint can be proved to be sound or otherwise; but the patient must be warned that if he has any trouble—the exact nature of which need not be suggested—he should not accept as inevitable the termination of his athletic career but should return without delay for further examination with the prospect that it will show the cause of his disability to be a condition which can be completely cured by a minor operative procedure.

(3) *There is a history of recurrent incidents with conclusive evidence on clinical examination of the presence of a torn meniscus.* This is the form in which most internal derangements due to damaged menisci are encountered. In the absence of outstanding contraindication the treatment is excision of the torn structure.

Lateral Meniscus

While tears of the lateral meniscus are less common than those of the medial meniscus, cystic degeneration is much more frequent and congenital anomalies are almost confined to the lateral side. The ratio of the incidence of lesions, computed from my own 1,650 cases which covers all types necessitating operation, is one lateral to two medial cases.

The symptoms and signs of tears are similar to those encountered on the medial side but with the difference that they occur in less positive form. The original accident is less definite, locking is less common, and incidents, because of the lax synovial attachments of the meniscus, may not be followed by effusion. Advice may be sought for little more than "trouble on the outer side of the joint," with vague symptoms of pain and instability and possibly the complaint of something "loose" or "clicking" on the outer side of the knee.

Treatment, as on the medial side, consists in excision of the entire meniscus.

Cystic Degeneration

Cystic degeneration of the menisci occurs as a result of trauma in the form of direct violence or abduction strain. It accounts for one out of eleven cases which come to operation; it is six times more common on the lateral side.

The patient complains of a dull ache on the lateral aspect of the joint which is greatly accentuated by any increase in physical activity. If the cyst is large he will call the examiner's attention to the presence of a swelling; if it is small, the size of a pea, he may be unaware of its existence. The characteristic feature of the swelling, which is usually situated immediately in front of the lateral ligament, is that it varies in size, depending on the position of the knee, reaching maximum dimensions in extension and decreasing in size on flexion.

Treatment, which consists in excision of the entire meniscus, results in complete relief of symptoms. Local excision, in the erroneous impression that the swelling is a ganglion, is followed by recurrence.

Anterior Cruciate Ligament

The anterior cruciate ligament is attached inferiorly to the anterior aspect of the tibial spine and inclines upwards, backwards, and laterally to be attached to the posterior part of the medial surface of the lateral condyle of the femur. Its function, as has already been mentioned, is the control of lateral rotation of the tibia in the terminal phase of extension.

In general the ligament may be injured: (1) *By abduction*—if the force is of sufficient magnitude to produce complete solution of continuity of the medial ligament, the anterior cruciate is invariably ruptured; in these circumstances the injury merges into insignificance in relation to the problem of repair of the much more important medial ligament (see below); and, more commonly, (2) *By derangement of the screw-home movement*—if the action of the ligament is to guide and control lateral rotation of the tibia in the last few degrees of extension, any attempt to extend the joint without lateral rotation of the tibia puts the ligament on the stretch. This is the reason for the close association between lesions of the medial meniscus and isolated ruptures of the ligament and the explanation of the finding that one in four cases from which a torn medial meniscus is excised shows a ruptured or attenuated anterior cruciate ligament.

Once the medial meniscus has been torn and has become liable to produce locking incidents, the anterior cruciate becomes vulnerable: if the footballer or athlete is in motion at the moment when the block to the screw-home movement takes place, the whole strain is thrown on the ligament and it ruptures. Furthermore, the commonest way in which the ligament is injured is when a bucket-handle tear has become displaced into the centre of the joint. Attempts to reduce the locking by forcible extension under anaesthesia take place at the expense of the ligament; and, in cases in which the displacement of the fragment into the centre of the joint becomes permanent, walking about, or otherwise attempting to produce complete extension of the joint, results in slow gradual attenuation and eventually to complete solution of continuity.

The symptoms of isolated rupture of the anterior cruciate ligament are giving-way or instability, especially at high levels of physical activity such as football, athletics, or modern military training. Undetected rupture of this ligament is the reason for any evil reputation meniscectomy may have attained amongst footballers and Service statisticians.

The classical physical sign of rupture is the ability to pull the tibia forward on the femur with the knee in semi-flexion.

A large number of ruptures of the anterior cruciate ligament can be prevented: once the medial meniscus

is torn and has produced locking, or is torn and is liable to produce locking, there exists a serious risk of rupture of the ligament, and the longer the torn meniscus remains in the joint, and the more violent the occupation responsible for the recurring incidents, the greater the risk.

A degree of instability which makes strenuous athletic pursuits impossible may produce little or no disability even in the occupations of heavy industry. If treatment is required it consists in the recognition that the quadriceps is a lateral rotator of the tibia in extension. If the amazing potential of the quadriceps for hypertrophy can be exploited it is possible to compensate to a very large extent for absence of the ligament.

Sprain of the Medial Ligament

Sprain or partial avulsion of the long anterior parallel fibres of the medial ligament at their attachment to the femur is one of the common injuries of the knee-joint. It possibly ranks third in frequency of occurrence to the minor injuries producing traumatic synovitis, the exact aetiology of which may be undefined, and the derangements due to damaged menisci. The significance of the injury lies not only in its frequency of occurrence but in the fact that it is so repeatedly misdiagnosed. If the recent injury goes unrecognized the common complication of the formation of heterotopic bone at the femoral attachment of the ligament, which gives rise to the "medial ligament syndrome" (frequently called Pelligrini-Stieda disease), is not anticipated, and the symptoms which follow are responsible for severe and prolonged disability.

The injury takes place as a result of a rotatory mechanism such as may occur in a minor skiing accident or on the football field. On examination pain, swelling, and tenderness are accurately located at the attachment of the medial ligament to the femur not far from the adductor tubercle. It is an extra-articular lesion, and unless the productive force has been violent there is no effusion. The injury is distinguishable from complete rupture by placing the ligament on the stretch by attempting to abduct the joint in extension : pain may be produced at the upper femoral attachment, but the stability of the joint is unimpaired.

Treatment consists in infiltration of the site of maximum tenderness with a few millilitres of local anaesthetic. Thereafter a 2-in. (5-cm.) square of sterile orthopaedic felt is placed over the area and a diverging spica of elastic adhesive bandage is applied to the joint with the object of promoting rapid absorption of the products of injury by elastic compression. This simple treatment may provide relief of pain and allow immediate resumption of weight-bearing and quadriceps exercises to be started.

Most sprains of the medial ligament present no difficulty and make a rapid and uneventful recovery. In a certain proportion of apparently simple cases, and especially those undiagnosed and untreated, the symptoms of pain and restriction of movement, instead of making the progress expected, become more accentuated with the passage of time ; and, the more strenuous the physiotherapeutic efforts to accelerate recovery, the greater the pain, weakness, and loss of flexion. These patients are usually found to be suffering from ossification of the haematoma at the site of avulsion. The presence of this complication can be confirmed with certainty by radiograph at the third or fourth week following injury. Once the diagnosis has been established it should be recognized that the lesion is to a large extent self-limiting, and that, provided the popular forms of aggravating the condition by massage, passive movement, or manipulation are avoided, recovery will slowly but surely take place. A small number of cases reach a final and completely quiescent state after a period of nine months with a disability due to loss of flexion. In such circumstances surgical intervention may be necessary to excise the bony mass which is interfering with the free movement of the ligament.

Rupture of the Medial Ligament

Complete rupture of the medial ligament is the most potentially disabling of the common ligamentous lesions of the knee-joint. The gravity of the injury lies partly in the importance of the medial ligament as an accessory stabilizing structure and partly in the fact that complete solution rarely, if ever, exists as an isolated lesion but is associated with rupture of the anterior, and even of the posterior, cruciate ligament, loss of the peripheral attachments of the medial meniscus, and fracture of the lateral condyle of the tibia ; all the associated injuries may coexist in the same joint.

The diagnosis may be suspected from the history, which, as has been indicated, involves considerable external violence. The injury is followed by severe, nauseating pain accompanied by the sensation of "something tearing" within the joint. The severity of the lesion usually compels the patient to cease work or leave the football field, but in this respect certain cases are misleading, as, in spite of the gross damage, the immediate disability may be less than that encountered in a torn meniscus.

If the capsule is ruptured, as it usually is, the effusion drains into the periarticular tissues. Therein lie a trap for the unwary and a common source of error ; a serious injury is unsuspected in the absence of effusion or haemarthrosis.

The final diagnosis must not be assumed until the presence of abduction in extension has been demonstrated. If pain and muscle spasm prevent the forcible manual abduction which is necessary to demonstrate whether there is complete solution of continuity or merely "overstretching," and to establish the condition of the cruciate ligaments by the drawer signs, "forwards" or backwards," or both, the examination should be performed under thiopentone anaesthesia.

When examination, on the lines indicated, demonstrates beyond shadow of doubt the existence of complete solution of continuity, the treatment of choice is operation. In incomplete lesions, or in the presence of technical contraindications to operation, conservative treatment in the form of immobilization in a skin-tight walking plaster cast, of the type which permits foot and ankle movement, is indicated.

Recurrent Subluxation of the Patella

The stability of the patella depends on : (1) integrity of the vastus medialis ; (2) absence of undue laxity of the capsular expansion on the medial side ; and (3) height of the lateral femoral condyle.

In many knee-joints which fall within the limits of normality an increase of lateral mobility of the patella may exist as a result of minor abnormalities of these

stabilizing factors. In such joints, and especially in the presence of a minor degree of knock-knee, medial rotation of the femur on the fixed tibia, or lateral rotation of the tibia on the fixed femur, may cause the patella to slip over the margin of the lateral condyle of the femur. If complete dislocation occurs the diagnosis is never in doubt, but lesser degrees of subluxation, in which the patella slips momentarily over the edge of the lateral condyle, are often missed. The complaints of locking, giving-way, pain, and effusion, being the same as those associated with meniscus injuries, may easily lead to an error of diagnosis. It is not an exaggeration of the situation to suggest that every internal derangement of the knee-joint in a female patient should be suspected to be a recurrent subluxation of the patella until proved otherwise : tears of the menisci in women are relatively uncommon.

On examination the most notable feature is wasting of the vastus medialis to a degree disproportionate to the severity of symptoms. The patellar tendon and medial capsule are lax, and mobility of the patella in a lateral direction is increased. It is well to remember that patients suspected of having a subluxation often display marked apprehension when the patella is pushed laterally in testing for stability or increased mobility.

Treatment is directed, if possible, towards the cause. In young people a knock-knee deformity may require correction by conservative or operative means. In older women, minor degrees may be treated conservatively by redevelopment of the vastus medialis. In many cases there is no alternative to operation, which normally takes the form of straightening the line of pull of the quadriceps by transferring the tibial tubercle together with the attached patellar tendon to the medial aspect of the tibial head.

Loose Bodies : Osteochondritis Dissecans

Loose bodies occurring in knee joints which are otherwise apparently normal are derived from either the articular surfaces or the menisci. For practical purposes, only those arising from the articular surfaces are of importance ; these are fragments from the margin of a condyle displaced into the joint immediately following a direct injury, or displaced into the joint after an interval of months or years, the condition known as osteochondritis dissecans. The aetiology of the latter entity has long been a matter of controversy and remains unsettled. My own view is that the lesion arises in joints of a particular anatomical type in which impingement of the tibial spine against the lateral aspect of the medial femoral condyle is possible, especially when forced extension occurs in the absence of synchronous lateral rotation of the tibia.

In the early stages, before the loose body has separated, the symptomatology is indefinite. There is often a complaint of vague pain, made worse by exercise, and an ache in the joint when at rest. There are recurrent effusions brought on by exercise but which rapidly subside with rest. When the loose body has separated, to these vague symptoms is added locking, which may be described as of a type which occurs "out of the blue."

The diagnosis can only be suspected on clinical examination. It is determined by radiography. Indeed, it is probably true to say that the radiographs which form part of the pre-operative investigation of every internal derangement due to a damaged meniscus, and which would ordinarily be expected to be negative, are taken largely with the purpose of eliminating oesteochondritis dissecans.

In young people, in whom the condition is detected before the loose body has separated, there are prospects of securing healing by immobilizing the knee in a plaster cast for a period of three months. In adults, and in those patients in whom the fragment has separated, there is no alternative to operative removal of the loose body. The long-term prognosis depends on the length of the history and on the size and site of the defect in the femoral condyle. If the defect is large and encroaches on a weight-bearing area, oestoarthritis may be expected to develop with the passage of time. The rate of degeneration and the degree of arthritis are directly related to the demands made upon the joint.

TENTH INTERNATIONAL CONGRESS ON INDUSTRIAL MEDICINE

The tenth International Congress on Industrial Medicine was held in Lisbon from September 9 to 17. This was the second such conference to be held since the war, the last being in London in 1948. Some 750 doctors and 50 nurses from 27 countries attended, and over 250 papers were presented. The work of the congress was divided into five sections, but the wide range of the papers submitted made it difficult always to trace the connexion between the subjects discussed at particular sessions.

Broadly, the papers fell into two groups: those confined to the narrow field of industrial accidents and occupational diseases, and those dealing with social, organizational, administrative, and educational problems.

Nickel and Cadmium Poisoning

In the former group there were a few communications which were of considerable, if limited, interest. Professor S. Forssman (Sweden) gave an interesting account of an outbreak of nickel fume poisoning, in which the haemorrhagic oedema encountered was indistinguishable from the clinical condition seen in nickel carbonyl poisoning. He had confirmed these observations in animal experiments.

Professor E. W. Baader (Germany) read an interesting paper on chronic cadmium poisoning. He pointed out that the use of this metal was increasing considerably, and it was to be found in the manufacture of alloys, in electroplating, and in the manufacture of alkaline electric accumulators. The symptoms of acute poisoning had long been recognized. Chronic cadmium poisoning, however, presented an entirely different picture, characterized by loss of smell, cough, and dyspnoea, with loss of weight ; examination showed golden yellow staining of the teeth, raised E.S.R., and the presence of an unusual protein in the urine, first described by Friberg. Post-mortem examination of a patient aged 39 who died of the disease showed a severe dilatation of the stomach, and several areas of segmental cylindrical distension and elongation, 8–12 cm. long, in the jejunum. Histological examination disclosed nuclear changes in the ganglion cells of the plexus of Auerbach and in the plexus of Meissner ; similar nuclear changes were found in the ganglion cells of the bronchial and tracheal walls. No changes were found in any other nerve cells. Professor Baader postulated a "neurogenic lung emphysema," and called for further observation in other countries. Dr. Lars Friberg (Sweden) confirmed the finding of emphysema in patients with chronic cadmium poisoning. He spoke also of the proteinuria found in these cases. He described some recent investigations that await publication, which strongly support the idea that the cadmium excreted in the urine is

linked with protein. He also asked observers in other countries to investigate carefully any cases of chronic cadmium poisoning which came their way.

Acrylonitrile and Benzol

Dr. F. Rieders and Dr. H. Brieger (U.S.A.), in a careful paper, drew attention to the greatly increased production of acrylonitrile, which is expected to increase fourfold in the next five years. For the first time a spectrophotometric method for the determination of acrylonitrile in air and in body fluids was described. Experiments with animals, including rhesus monkeys, demonstrated the formation of cyanide and cyanmethaemoglobin, as well as the excretion of thiocyanate following measured absorption of acrylonitrile. The typical effects of anoxia were demonstrated by histological findings in the brain.

An interesting paper was contributed by Dr. J. Bousser, Dr. C. Albahary, and Dr. S. Tara (France) on some atypical effects of benzol upon the blood. The minor forms included lymphocytosis in the region of 12,000 to 15,000 per c.mm., or a leucocytosis (in the absence of infection) greater than 12,000 per c.mm. Either of these findings should require the workman's removal from exposure. The major manifestations included the leukaemias—both myeloid and lymphocytic had been observed.

Dust Diseases

A number of papers were devoted to dust diseases. These included an interesting group of contributions by the Medical Research Council's Pneumoconiosis Unit (Great Britain). Dr. A. L. Cochrane reported studies on the epidemiology of simple pneumoconiosis in coal workers. Results showed no clear evidence of any simple relationship between attack rate and total dust dosage, or the total free silica dosage. It was pointed out that this did not mean that such a relationship did not exist, but that some other method of studying the problem should be evolved. This would involve studying the rate of progress of the disease in miners whose exposure to dust could be accurately assessed. This was not possible until both radiological and dust sampling methods were much improved. To design a satisfactory dust sampler considerable basic knowledge was required. Dr. I. Davies gave the acceptance curve for dust particles which should be aimed at in designing a dust sampler, if it were to imitate closely the human lung. Dr. B. M. Wright described experiments carried out on rats, which were planned to discover whether *concentration* × *time* is a satisfactory measure of the amount of dust that will be inhaled and retained in the lungs. Previous observers had suggested a critical level below which dust accumulation in the lungs did not take place. His experiments did not confirm this view, however, and suggested that *concentration* × *time* was a satisfactory measure. These and other experiments have made it possible to design a dust sampler with which it is hoped an accurate and physiologically significant assessment of dust exposure will be possible.

Occupational Cancers

Papers on occupational cancers dealt with various aspects of this difficult subject. Dr. W. C. Hueper and Dr. T. F. Mancuso (U.S.A.) discussed survey methods used in the United States to study the relationship between occupation and cancer at various sites. Papers dealing with the better-known conditions were given. Dr. T. S. Scott (Great Britain) reported a series of 67 patients with bladder tumours, 30 of whom had worked exclusively at either benzidine manufacture or handling. He showed that the latent period (time between first exposure and appearance of tumour) in these patients was similar to that found in patients who had been exposed to β-naphthylamine. In each group this period was longer in the handlers (whose exposure was less) than in the manufacturers. He maintained that this series was sufficient proof, if any were still needed, of the carcinogenicity of benzidine. He called for the exercise of the greatest care in the manufacture and handling of benzidine. In Europe the manufacture of β-naphthylamine had been stopped; the manufacture of benzidine should be continued only under the best possible conditions. These findings were supported by German and Italian speakers. Dr. G. di Maio entered a passionate plea for the routine cystoscopic examination of workers exposed to all cancer-producing aromatic amines.

Development of Industrial Medicine Services

Many papers were concerned with the development of industrial medicine in different countries, and with the administrative and educational problems that arise in consequence. Professor P. Mazel (France) outlined the position in France, where since 1946 there has been a statutory requirement on industry to engage the services of a doctor. The duties of the French industrial medical officer included the supervision of young entrants and those workers about to return after long absence resulting from illness or accident. His main work, however, was concerned with the working conditions in factory, mine, and shipyard. General practitioners did this work, but a special training was regarded as essential and was encouraged by entitling the doctor to a higher scale of fees.

In other countries the development of such precise legal requirements was lacking, but in many there was evidence of a rapid development of industrial medical and nursing services. Professor Alfonso de la Fuente Chaos (Spain) reviewed the philosophical as well as the technical requirements of those who entered this branch of medicine, and gave in detail the syllabus of the year's training course proposed for industrial doctors in Spain. Dr. L. Noro and Mlle. R. Sayrajari dealt with the training problems of doctors and nurses in Finland, where special courses are required. Miss H. Neep described the preparation of the nurse for industry in Great Britain, and Dr. T. G. Faulkner Hudson (Great Britain) gave an outline of a short practical course used in Bristol to introduce doctors and Service medical officers to industrial health.

Rehabilitation

Professor W. Leblond (Canada) reviewed some of the social aspects of rehabilitation. He pointed out the economic as well as the social advantages to be gained from a sound national policy on this aspect of treatment. From his experience in Canada he had arrived at conclusions which in no way differed from those now generally accepted in this country. He raised the difficult problem of the resettlement of the tuberculous, and opposed "unfair and non-beneficial segregative measures." He emphasized that the selection of a new training for a handicapped worker must not be decided simply by labour shortages and physical capacity, important as these were, but should also have regard to the legitimate aspirations of the workman himself.

Professor J. M. Porto (Portugal) dealt with the special problems of the cardiac patient. He regarded the assessment of the capacity of these patients in properly equipped cardiac clinics as essential, but viewed the proper training and placement of these patients as constituting the most important part of treatment.

Portuguese Hospitality

Those who attended the congress could not fail to be impressed by the magnificent hospitality provided by their Portuguese hosts. Lisbon is a fine centre for such a meeting, and the arrangements at the Instituto Superior Técnico were of the highest quality. This was in fact very necessary, since on more than one occasion papers were still being delivered at midnight, though it is true that this was made necessary by social activities earlier in the day. British delegates will remember the congress particularly for the delightful entertainment offered by their Portuguese colleagues, for the opportunity to meet old friends from distant parts in warm, bright sunshine, and for evidence of a world-wide growth of interest in occupational health.

CHARTERED SOCIETY OF PHYSIOTHERAPY

ANNUAL CONGRESS IN LONDON

The annual congress of the Chartered Society of Physiotherapy was held in St. Pancras town hall from September 27 to 30. It was opened by Sir JOHN CHARLES, Chief Medical Officer, Ministry of Health, who described medical care in all its elaborations as one of the most expensive commodities in the modern world, alike in time, money, and man- and woman-power. Nevertheless, there was an impressive other side to the balance-sheet, and the shortening of illness, prolongation of active life, and postponement of death meant an unassessable but overwhelming credit balance. Of physiotherapists he said that there was no prospect of their under-employment. Physiotherapy, like nursing, was a handmaid of medicine, and would surely maintain and expand its complementary relationship.

The congress then entered upon a programme of lectures and practical demonstrations, with visits to a number of hospitals and other institutions. Several of the lectures were on special techniques. Professor W. R. Spurrell discussed precision of movement, Dr. J. N. Barron gave an illustrated exposition of plastic surgery, especially skin-grafting, Professor A. E. Ritchie dealt with the question of whether electro-diagnosis was a routine or a research technique, and Mr. A. Dickson Wright discoursed on venous thrombosis and showed a film. The founders' lecture, on "Rehabilitation," was delivered by Professor J. Whillis, chairman of the Society's council.

Neglect of Massage and Manipulation

Dr. J. H. CYRIAX discussed the present position of physiotherapy. The subject, he said, had evolved in three phases. During the first period accuracy in treatment counted for very little. Painful conditions were apt to be treated by radiant heat and massage, directed largely to where the pain was felt. This phase lasted from the earliest days of physiotherapy until about 1940. In the second period exercise therapy and penetrating treatment by deep heat were put on a solid foundation, and indications and technique were brought to a high pitch of exactitude, but massage and manipulation continued to be neglected. Here, said Dr. Cyriax, there was a vast field as yet untouched by physiotherapists. It was not by shirking their responsibilities and leaving numberless traumatic cases to their lay competitors that their status would be brought to its proper level; they must never accept a position inferior to the self-styled bone-setter. Careful undergraduate instruction was needed, and this in the case of deep massage and manipulation was not given. The present policy was to abandon to laymen patients with lesions calling for manipulation. It was no pleasure to doctors to search in vain for physiotherapists able to administer correct manual methods before reluctantly recommending osteopathy. It was up to physiotherapists to alter that situation. By using methods which brought swift relief and were unobtainable elsewhere the physiotherapist would soon establish a reputation and the happy era of full accuracy in all aspects of physiotherapy would begin.

The Society's Dinner

The MINISTER OF HEALTH was the principal guest at the Society's dinner with which the congress concluded. He said that in his experience every hospital where there was a well-directed and organized physiotherapy team was a happy hospital.

"The creation in the patient of the will to be well is one of the significant developments of modern medicine, and in such creation physiotherapy plays an extremely important part. The physiotherapist is concerned, not merely with regenerating muscles which have fallen into disuse or have sustained injury, or with enabling a patient to get back to a job, but, with her enthusiasm, inspiration, and cheerful patience, in helping in a very large measure to create that will to be well. In many cases that is the most important thing she does."

Mr. Marquand added that he hoped to see rehabilitation centres rapidly established throughout the country, not merely because they would reduce the occupancy of beds by chronic cases, but because they would be a means of returning fully rehabilitated persons to play their part in the normal life of the community.

Sir HARRY PLATT, the president of the Chartered Society, presided at the dinner, and proposed the health of the guests, who, in addition to the Minister, included the Dean of St. Paul's, the Chief and Deputy Chief Medical Officers of the Ministry of Health, the congress lecturers, and delegates from the Dominions. Mr. A. DICKSON WRIGHT proposed the health of the Chartered Society—a body of 16,000 women and rather under 1,000 men—and discovered the earliest physiotherapist in history to have been Abishag the Shunammite, "the fairest girl in all the bounds of Israel," who was called in to attend King David in his last days. Professor J. WHILLIS, in responding, said that the Society, along with certain of its sister societies, had recently had its case considered by the "doctor" appointed by the Minister (an allusion to the Cope Committee). Patients did not always like the advice given them, and the "doctor" had made suggestions for the health of the Society which perhaps it did not altogether like. They hoped that if there was a consultation the specialist called in would succeed in adjusting matters to the satisfaction of both sides.

A further toast was given to the founders of the Society, in particular the four women, with Dorothy Paget at their head, who in 1894 established the Society, secured the good will of the medical profession, and, the following year, instituted the first examination.

THE LADY WITH A LAMP

At the end of this well-intentioned and oddly dull film we have had a bit of everything—waltzes, the House of Commons, crinolines, guns, suffering wounded, the Queen, joking wounded, horse-drawn vehicles, obstructive doctors, and a heroine. But we have learnt little more about the legendary Lady with a Lamp. There is no need to conjecture about Miss Nightingale's character. Her lifelong habit of writing thousands of private notes about her feelings has made available a mass of data revealing her complex character, as her memoranda her genius for organization. We can know all her feelings from 1837, when God called her, though she did not know to what, through the 16 years of intense internal struggle and the shorter struggle with her family, till in 1853 she emerged, an open though decorous rebel, as head of the Hospital for Poor Gentlewomen. In October, 1854, she left for the Crimea; in 1856 peace was declared, and in those 18 months she had achieved three momentous things: she had become—how rightly—a national heroine, and she had changed for ever in the public mind the pictures of the soldier and the nurse. There followed years of work in which she consolidated and extended her revolution in hospital nursing and in the Army medical services.

To show the development of such a woman and then to show her in action, to show systems as they were before and after her work, requires a most selective and economical use of material and a concentration on the main character. It also requires a grip of essentials: often, however, the film gives the trivial. To show a hospital as it then was (for example, in a famous London hospital the nurses slept in wooden cages on the landings) would have shown better the difficulty of a decent woman nursing than Mrs. Nightingale's nearly swooning at a dinner party because her daughter uses the word "prostitute." Moreover, there are many irrelevances and distractions taking valuable time and space that might have been given to Miss Nightingale—a misty

and symbolical Charge of the Light Brigade with Tennyson's words superimposed; many more Cabinet meetings than are necessary to show the political importance of the issues. One suspects that much space is given to the Roebuck vote of censure for the sake of the spectacle of the House of Commons. It is true that the political scenes show Sidney Herbert, her friend and supporter, but in fact his value lay in his being her mouthpiece and servant. Yet in the film facts are altered to make him seem the originator when she was. This slurs over the driving and dominating nature behind the gentle manner. Miss Neagle's farewell to the Crimean dead is wholly emotional and omits the characteristic, "73% in eight regiments in six months from disease alone," following the, "Oh, my poor men, I am a bad mother to come home . . ." When Miss Neagle speaks to the Purveyor with threatening power the film comes alive, but only momentarily.

Inside this rather unreal conception the acting is uniformly sincere and good.

LORD HORDER AT KING'S COLLEGE HOSPITAL

At the opening of the session ceremony at King's College Hospital Medical School on September 28 the address was delivered by Lord Horder. Referring to the new regulations of the University of London, Lord Horder recalled that his plea had always been that anatomy, physiology, chemistry, and physics should be directed towards the actual examination of the patient, and he thought it was a step backwards when the academic anatomist, physiologist, chemist, or physicist was put in charge of training. He remarked that he still met doctors who had never clearly seen the optic disk.

Medicine, Lord Horder continued, was the science and art of healing. The importance of prevention was now stressed, but that was implicit in the definition. If doctors were asked not only to cure but to keep the fit person fit and to make the near-fit fit, there were two prerequisites. The first was that the doctor must know all about the mind as well as the body of his patient. The other was that more attention should be given to providing the basic elements for maintaining health—enough of the right food, warmth, shelter, access to sun and air, a satisfactory job of work, and leisure and the amenities connected with leisure. "This prerequisite is the business of the State, centrally or locally, and not the doctor's business. There is a feeling that the doctor is responsible for the whole health of the whole nation. That is a false idea."

If the contact with the patient which was afforded by general practice did not appeal to the temperament of the student, he could now still find his niche in medicine. "If you do not like human beings overmuch you can stick to your *x* rays or your microscope." But the business of new branches of medicine needed to be watched carefully. He was not sure that the underlying conception of social medicine justified itself. Consideration of the ultimate as well as the intimate causes of disease did not mean a new but only an extended conception. It was good to study the patient's environment; such knowledge had always been pertinent, though it had been neglected. But to elevate inquiry about these things into a special branch of medicine was, in his opinion, redundant. He would say the same of the effort to make psychosomatic medicine a new concept.

Lord Horder added that he had not been favourably impressed by the "new look" which was assumed by the practice of medicine in this country whereby doctor and patient were enabled to meet so seldom and for so short a time. He believed that the State should give every facility to doctors to function in the consulting-room, the home, the hospital; that the hospital services should be regionalized, and opportunity taken to rationalize them, and that medicine should be made available to every citizen. But in his creed it was "our medicine," not medicine as conceived by and purveyed through a bureau. Some thought that with a little more humility and consultation the "new look" might have been quite attractive. He thought they were right.

Plans for Extending Hospital and Medical School

The Dean of the School (Dr. Vernon F. Hall) spoke of the project for extending the School by building a new six-story block. This would enable the annual intake of students to be increased from 50 to 70, as well as providing extra room for the present number and for research. The board of governors had their own plans for increasing by 300 the number of beds on the Denmark Hill site. The School also proposed to establish clinical professorial units in medicine and surgery, complementary to the existing chairs in pathology, to augment and not replace the present method of teaching clinical subjects by part-time consultants, and also to co-ordinate research. Sir Charlton Briscoe had made a gift of £1,000, and at his suggestion an annual prize would be offered for research carried out in the previous year by a member of the staff of the hospital or school or a student or former student.

MIDDLESEX HOSPITAL

AN INSTITUTE OF EXPERIMENTAL MEDICINE

The establishment of a new institute at the Middlesex Hospital was announced by the Dean, Sir Harold Boldero, at the annual dinner of the School, which took place on September 28. He hoped that this institute, which would be opened in the present session, would be named the Institute of Experimental Medicine. No other medical school in this country had quite the same concept of what was meant as was envisaged at the Middlesex. A building at the rear of the School would be converted into a laboratory and made available solely for clinicians wishing to do clinical research. Men and women practising medicine, if they had an idea, would thus have the opportunity of taking that idea to a well-equipped laboratory, where they would be given space, time, and facilities for carrying out the research to which it gave rise. This institute was due to the wisdom and foresight of the board of governors, who would make a substantial contribution to its maintenance from the endowment funds.

In a reference to the difficulty which students of the undergraduate medical schools in London experienced in "getting together," Sir Harold Boldero mentioned the success of a clinical "at home" at the Middlesex this summer. The idea had arisen from Guy's the previous year, and had been elaborated. Students from all the other Metropolitan medical schools were invited, and the proceedings ended with an enjoyable dinner provided by an anonymous member of the board.

The chair at the Middlesex dinner was occupied by Dr. D. Evan Bedford, who mentioned that there were now 2,300 persons on the hospital's pay-roll. The Ministry had "axed" their budget, and at the same time had asked them to increase wages. Dr. Bedford quoted Oscar Wilde's advice, "Don't buy things you don't want simply because they are expensive." Since the National Health Service came in the thirst of the public for medicines had become almost insatiable, and was now costing nearly as much as the general-practitioner services. Speaking of developments in the hospital, the chairman said that the *x*-ray department and observation wards had been extended and a new occupational therapy department had been built. The new cardiology department would have first priority, and the hospital had reached its century in "blue baby" operations. He congratulated Dr. Douglas McAlpine and Dr. S. Handley on the new *Archives*. Last year he had mentioned

that the first woman student of the School had qualified; now they had the first lady Broderip Scholar.

The senior Broderip Scholar, Dr. E. D. ACHESON, reviewing the lighter side of the School's activities, mentioned the exploit of two of the students in winning the canoe race from Devizes to Westminster in record time. The toast of "The Chairman" was proposed by Mr. PHILIP WILES.

NEW MEDICAL CENTRE AT LONDON DOCKS

GROWTH OF PORT MEDICAL SERVICES

The MINISTER OF LABOUR AND NATIONAL SERVICE (the Rt. Hon. Alfred Robens, M.P.) opened on September 28 the first full-size medical centre in the Port of London, at the Royal Albert Dock. The Dock Labour Board is now operating as part of its welfare activity twenty-nine medical centres in various ports, but hitherto only one of them has been established in London. This, a small-scale centre in adapted premises at the Surrey Docks, has given 3,000 treatments during the first six months of its operation.

The new centre at the Royal Albert Dock is a more elaborate establishment, constructed according to one of four master plans of the Board designed to meet the requirements of various ports. It includes a large surgery with equipment for the immediate treatment of injuries and minor ailments, waiting-room, rest-rooms, and rooms for doctor and nurse. The staff consists of two trained nurses under the supervision of a medical officer. It is housed in a pleasant building, surrounded by a garden which the men of the Royal Docks have volunteered to plant and maintain in their own time and at their own expense.

The point is stressed that the medical centre is not a mere first-aid station. It is intended to be used after a casualty has already been given first-aid nearer the scene of the accident. It in no way supersedes the first-aid service available in the small rooms which are being opened in the docks and ports, or dispenses with the need for trained first-aid personnel amongst the dockers themselves. The centre is equipped for dealing with the continued treatment which may be necessary for some time after an accident and for the treatment of the various minor ailments which may occur in the working day. It incorporates experience already gained at other ports such as Southampton and Liverpool, and it is hoped that it will be a model, setting the standard for future installations for the physical welfare of all who work in ports, not only dock employees in the strict sense of the term.

Relationship to N.H.S.

It was also stated emphatically by those concerned that in this development of the port medical service there is no desire to create a substitute for existing medical services, whether provided by the National Health Service or by private practitioners outside the Service. What emanates from the dock medical service is essentially an industrial service provided by the employers for the benefit of their workers in connexion with their employment. The new medical centre is indeed like a factory medical centre of the first class. The Dock Labour Board is fully alive to the importance of co-ordination and co-operation between the port medical services and the National Health Service and the need to avoid duplication. The two services are regarded as really complementary, and it is emphasized that there need be no more overlapping between them than, to use Mr. Robens's phrase, there is in the seams of a garment. Many dock workers no doubt will go to the centre for daily treatment during the lunch break and thus avoid loss of working time. The medical staff of the centre may find it necessary in some cases to advise a man to see his own doctor if the nature of his trouble indicates that that is the best course for him to take. It is understood that the relations between the existing port medical services and the doctors and hospitals engaged in the National Health Service are friendly and co-operative. Mr. Robens described the port medical services as being, like the factory medical services, in the nature of outposts, while the main line of defence against sickness or injury is the National Health Service.

Origin of the Service

A word may be added about the history of medical centres for dock workers. These were first set up in Liverpool, Birkenhead, and Glasgow early in the last war. By the end of the war there were four medical centres in Liverpool, one in Birkenhead, and six in Glasgow. In addition to the 29 now in operation in 16 ports, the building of 18 other centres in 10 ports will be completed shortly. A similar centre to the one at the Royal Albert Dock is nearing completion at the West India Dock, and additional centres are being planned for the other royal docks, the London Docks, the Tooley Street wharves, and Tilbury. During the first half of 1951 the 28 centres in operation gave just upon 124,000 treatments.

At the opening ceremony tribute was paid to the man to whom this development was due—the late Mr. Ernest Bevin. It was his idea when he was Minister of Labour in 1941 to set up in the vicinity of the docks a service of medical advice and treatment similar to the factory medical service, and the first centres on Merseyside and Clydeside followed.

THE KING'S HEALTH

Below we print the bulletins on the King's health issued since Tuesday, September 25, at 11 a.m. All these bulletins have appeared over the signatures of the same five doctors, namely: Sir Daniel Davies, Sir Horace Evans, Dr. Geoffrey Marshall, Mr. C. Price Thomas, and Sir John Weir.

Tuesday, September 25, at 7.15 p.m.:

The King has had a comfortable day and has been able to take some nourishment.

Wednesday, September 26, at 11 a.m.:

The King has had a less restful night, but his Majesty's general condition this morning is good and progress is maintained.

An unsigned statement was issued from Buckingham Palace at 6 p.m. the same evening, which read:

In connexion with the medical bulletins issued periodically from Buckingham Palace, it should be remembered that, while the King's gradual progress towards recovery has been uninterrupted and although no complications have arisen so far, there will inevitably be a period of some anxiety for the next week or 10 days.

Thursday, September 27, at 11 a.m.:

After a better night the King is stronger, his appetite is improving, and progress continues.

Friday, September 28, at 10.30 a.m.:

The King has had another comfortable night and is making steady progress.

Saturday, September 29, at 11.15 a.m.:

Six days have now elapsed since the operation on the King. This has been a period free of complications. His Majesty is gaining strength daily.

Sunday, September 30, at 11.15 a.m.:

The King's progress continues.

Monday, October 1, at 11 a.m.:

There has been further improvement in the King's condition during the past 24 hours.

Tuesday, October 2, at 11.30 a.m.:

The King has had a good night, and his general condition this morning is satisfactory.

Correspondence

Inheritance of Defects

Sir,—In your issue of September 22 (p. 727) Professor A. G. Watkins writes of a group of congenital defects "of hereditary and familial aetiology—for example, achondroplasia and acholuric jaundice." While it is true that about half the children of achondroplasic dwarfs are achondroplasics, the majority of such dwarfs (in Denmark about 80%) are the children of normal parents with no family history of the condition. Most of them die in their first year, and achondroplasic women cannot bear a child without caesarean section, so the condition is rarely inherited for more than one or two generations. Most cases are due to mutation. We do not know the cause of these mutations. They may be due to natural radiations, to mutagenic substances, or to unguessed-at causes. But to speak of hereditary aetiology in such cases is liable to cause quite unnecessary fear among their relatives. A predisposition to acholuric jaundice is, on the other hand, usually inherited from a parent.

Kemp in particular has stressed the importance of mutation as a cause of disease, and it is, I think, of some importance that physicians whose advice may be asked in such cases should become familiar with the notion that an abnormality may be hereditary in the sense that it may be handed down to descendants, without being hereditary in the sense that it was derived from an ancestor.—I am, etc.,

London, W.C.1. J. B. S. Haldane.

Correct Dose of Digitalin

Sir,—My attention has recently been drawn to the fact that substantial numbers of tablets of digitalin are being prescribed in doses so small that they cannot possibly have any therapeutic effect. The confusion has no doubt arisen because the powerful glucoside digitoxin, which can produce full digitalization in doses as small as 1.0 mg. (1/64 grain) is also called digitaline crystallisée (Nativelle's digitaline). Digitalin without the final "e" is a mixture consisting mainly of the relatively inactive glucoside, digitalinum verum. It is described in the *British Pharmaceutical Codex*, and doses by mouth and injection are given. The effective single oral dose is 32 to 64 mg. (½ to 1 grain), and even so it must be given frequently, since it is relatively rapidly excreted. The dose by injection is 4 to 12 mg. (1/16 to 1/5 grain), and it is probably retained in the *B.P.C.* because it is relatively water-soluble and can be given subcutaneously.

It is singularly unfortunate that manufacturers in this country list tablets of digitalin only in strengths of 0.1, 0.24, and 0.6 mg. (1/600, 1/250, and 1/100 grain), all of which are ineffective doses unless about 50 tablets are administered. It appears that these are the usual strengths prescribed, and tablets containing the full *B.P.C.* doses are very rarely ordered. One large firm of manufacturers informs me that they have never received an order for any strength higher than 6 mg. (1/10 grain) for oral use and 0.6 mg. (1/100 grain) for hypodermic use.

It is to be hoped that those who wish to prescribe digitoxin *B.P.C.*—i.e., digitaline crystallisée—will make this clear in their prescriptions. If, as seems unlikely, it is really intended to give digitalin, then the dose should be of the order of ½ to 1 grain. Manufacturers will, of course, make tablets of this strength only when prescriptions for them are received by retail pharmacists.—I am, etc.,

Sheffield. E. J. Wayne.

Danger of Extracting Many Teeth at Once

Sir,—May I draw attention, through the courtesy of your columns, to the apparently increasing practice of removing comparatively large numbers of teeth at one sitting? I do not refer to routine clearances for the satisfactory fitting of dentures, but to patients who have been referred for dental extraction by their medical practitioners, presumably for some abnormal physical condition. The following three cases have recently been admitted to my wards:

1. A woman aged 43 with a history of rheumatic fever at the age of 12 had been complaining of recurrent diffuse muscular pains, thought to be of a fibrositic nature. She was referred by her doctor to a dentist for teeth extraction as a form of treatment for her "rheumatism." She had 17 teeth extracted at one sitting under local anaesthesia, and two hours later began to develop pain in the face and right ear, swelling of the upper jaws, and a swelling in the submandibular region. These symptoms and signs increased, and on the fourth day her condition was sufficiently serious for her to be admitted to hospital. She was an ill woman, pulse 128, temperature 102° F. (38.9° C.), with massive bruising of the left eye, both cheeks, and both lower jaws, and a large tender swelling below the mandible. The gums were lacerated and infected, and the tongue displaced upwards by a sublingual swelling. She had the appearance of a severe street accident. Blood count showed haemoglobin 11.5 g. (78%), white cells 11,000 per c.mm., with normal differential count; bleeding and clotting times normal.

2. A man aged 40 had been complaining of a progressive mild polyarthritis for three months. He had "rheumatic fever" at age 11; no details were known of this illness. His doctor referred him to a dentist for treatment. The dentist informed the patient that the gums were infected and extracted 22 teeth in two sessions. Ten days later the patient found his knee swollen, red, and painful, and was unable to walk. Soon all his joints became acutely involved, and he was admitted to hospital with a very severe generalized acute arthritis; temperature 100° F. (37.8° C.), pulse 100, and a few red cells in the urine. In addition to his acute exacerbation he may well have begun a bacterial endocarditis.

3. A man aged 23 was advised by his doctor to "have his teeth looked at" owing to a complaint of "rheumatism in the neck and arms." He had 14 teeth removed, for pyorrhoea, in one session. He was admitted to hospital three weeks later complaining of malaise, fever, and increase in pains, with swelling of his peripheral joints. Investigation showed that this patient had a subacute bacterial endocarditis.

Although, of course, it is well known that these effects may be associated with dental extractions, I suggest that in view of these cases a medical practitioner referring patients with some physical illness which he believes may be relieved by dental extractions should be particularly careful to tell the patient, or preferably the dental surgeon, that not more than two or at the most three teeth should be removed at one operation. This seems to be of particular importance if a history of "rheumatic" disease, either articular or non-articular, is obtained.—I am, etc.,

Ashford, Middlesex. A. Barham Carter.

Treatment of Rheumatoid Arthritis

Sir,—In their interesting article, "Hypoglycaemia in Treatment of Rheumatoid Arthritis," Dr. G. D. Kersley and others write (September 8, p. 576), "No definite conclusions can be drawn from our findings on the mode of action of hypoglycaemia in rheumatoid arthritis." This seems fortunate, as there is no convincing evidence in their two publications that insulin hypoglycaemia has a specific action in rheumatoid arthritis.

In 72 cases treated by hypoglycaemia 82% were improved temporarily; of 22 control cases 78% improved. This difference is not statistically significant. Of the 72 treated cases 44% were markedly improved; of the 22 control cases 14% were markedly improved. This difference is significant, and the probability of it occurring by chance is less than one in a hundred; and would mean that hypoglycaemia does have a specific action in rheumatoid arthritis, if care had been taken to see that other factors than chance were not affecting the observations. This precaution does not appear to have been taken.

A quick procedure to exclude such factors as case selection is to choose the cases for treatment and control at random, and the number of controls will then approximate to the number of treated cases; with a proportion of 22 control cases to 72 treated cases it seems unlikely that any such precaution was taken.

"The method of clinical assessment was similar to that previously reported" (*British Medical Journal*, 1950, **2**, 855) and included observations on the general feeling of well-being, mental outlook, subjective pain (including rest pain), swelling, range of movement, deep hyperalgesia, in addition to functional ability. This conglomeration of observations depends, with the one exception of swelling, on subjective factors, and the nice distinction between "improved" and "markedly improved" may well have occurred as a result of suggestion or subconscious prejudice in the observer. It was pointed out in the *British Medical Journal* (1950, **2**, 875) that insulin hypoglycaemia cannot be given without at least the patient being aware that something unusual has occurred; and this awareness must be communicated to the assessor, so that if he is prejudiced in favour of the treatment under test he may be subconsciously influenced in his assessment. These investigators make the observation that a second course of treatment had less effect than the first. There are several hypotheses that would fit this phenomenon; the one that first leaps to the mind is that it is a dying-down of the psychological effect of any new therapy.

The gain in weight observed does not of course necessarily bear any relation to anti-rheumatoid activity and, as these workers point out, was not related to the previous loss.

There was a "tendency" for the E.S.R. to fall, but these observations were not paralleled with a control series, so that this tendency may have been greater or less in the untreated cases, and the observation as it stands is of no significance.

The fall in circulating eosinophils does not necessarily imply anti-rheumatoid activity and may occur after an injection of adrenaline or even after an injection of distilled water (Abelson, D., and Moyes, E. N., *Lancet*, 1950, **2**, 50), and has been demonstrated (Roche, M., *et al.*, *New Engl. J. Med.*, 1950, **242**, 307) in the apprehensive period prior to a surgical operation.

These criticisms can never destroy the observations made, but are levelled at the interpretation. The criticisms do not prove that hypoglycaemia never has a specific action in rheumatoid arthritis, a null assumption which can never be proved by experiment, but which may one day be disproved; but they do show that at least one other explanation would equally well explain the reported facts; that is, that the psychological effect of a new therapy—and a somewhat dramatic one—was being observed, and not a specific action of insulin hypoglycaemia. It is unfortunate that the experiments were not so planned as to differentiate between these two possibilities. There is an interesting field for this team of spa workers to solve this problem, and to investigate their discovery that a second course of insulin hypoglycaemia does not work as well as the first.

Robert Boyle wrote, "You will meet with several observations and experiments which, though communicated for true by candid authors or undistrusted eye-witnesses, or perhaps recommended by your own experience, may, upon further trial, disappoint your expectation, either not at all succeeding constantly, or at least varying much from what you expected."—We are, etc.,

Flimwell, Kent. GEOFFREY E. LOXTON.
DAVID LEVAY.

SIR,—Arising out of the interesting paper by Dr. J. Goslings and his colleagues (September 22, p. 698) it may be pertinent to record two cases of rheumatoid arthritis entirely resistant clinically to A.C.T.H. Neither case showed clinical evidence of adrenal abnormality and both gave normal responses to the Thorn and Kepler tests. One showed no clinical response to cortisone (500 mg. in a day), while the other was improved. Both cases suffered from typical severe rheumatoid arthritis of two and four years' duration respectively, with sedimentation rates ranging between 50 and 120 mm./hour. Doses of A.C.T.H. up to 400 mg. per day intramuscularly or 100 mg. intravenously were finally employed. The addition of thyroxin or ascorbic acid did not influence the result, and three different batches of A.C.T.H. were tried.

It was felt that these results help to confirm our previous impression that the "rheumatoid blanketing" factor is distinct from the "eosinopenic" factor. Perhaps this is explained by Young's recent work (*Lancet*, 1951, **1**, 1211) in which he produces evidence that there are two distinct pituitary principles that can affect the adrenals.—I am, etc.,

Bath. G. D. KERSLEY.

Backs

SIR,—Every practitioner must be aware of the enormous increase in the number of cases which I choose to term "backs." Some, of course, are disk lesions, others less serious displacements—or are they infections? It would be interesting to have these cases made notifiable and gain some idea of how many such cases there are in the country at the present time. It is significant that when I mentioned the subject to a patient the other day she replied, "It is funny you should talk of this; we have three cases in our office in plaster."

I have, of course, had many cases and sought the advice of various experts. They will diagnose the condition—but no one can explain the enormous increase in the number of cases. The condition usually starts with some quite minor movement—apparently not sufficient to displace a disk or cause a propulsion unless there is a predisposing cause.

Is this predisposing factor possibly infective, dietetic, or due to a refining process in the preparation of some article of food?—I am, etc.,

London, S.W.1. W. DESMOND URWICK.

Rupture of the Spleen

SIR,—May I add two further cases of ruptured spleen to those quoted in your correspondence columns? I cannot believe that this injury is seen so uncommonly in British hospitals; certainly a case such as the first I quote must be expected within the experience of most house-officers. Having no clinical notes available, my notes are confined to details accurately remembered. Both cases occurred in the teaching hospitals of Birmingham.

(1) 1948. A healthy man of some 25 years, cycling home from early morning church, skidded in the rain and was thrown from his bicycle, his anterior lower ribs on the left side hitting the kerbstone. He was momentarily unconscious, and, being within 100 yards, was brought to hospital. When first seen he was fully conscious, presented no abnormal neurological signs, and merely complained of headache and bruised ribs. He wanted to go home, but was prevailed upon to stay for a skull radiograph—a routine matter. On rising from the radiographic table about two hours after the accident, he complained of severe upper abdominal pain and a feeling of faintness. A diagnosis of ruptured spleen was made, and confirmed at operation, when it was removed. The tear in the organ was parallel with the gastro-splenic omental reflection. It should be noted that when first examined the abdomen appeared normal—the well-known "silent period."

(2) 1949. A small boy, aged about 6 years, was admitted to the casualty department, having fallen from a low first-floor window to the ground, a distance of about 14 ft. He had been unconscious, and was semi-comatose on admission. He had a contusion and laceration of the forehead, but no other neurological signs. He became normally conscious in a short while, and complained only of headache. *X*-ray examination of the skull revealed a frontal fracture. His abdomen was examined by me and appeared normal. He was referred for admission to the neurological department, and the neurosurgical registrar examined him in my presence, again finding nothing abnormal in the abdomen. He was admitted and again examined by the neurosurgical house-officer.

It was noted that he had passed a restless night, and in the morning, some 18 hours after the accident, his abdomen was found to be tense, tender, and with signs of free intra-abdominal fluid. He quickly collapsed, but responded to transfusion. A few hours later he was fit to undergo laparotomy, when a ruptured spleen was removed.

My recollection fails me as to the figures of his blood pressure when first noted, but it was considered to be within normal limits. A disappointment, this—for the natural

interpretation of the long "silent period" is an initial depression of the blood pressure due to cerebral trauma; the remarkable feature of the case being the way the bleeding seemed to occur before the eyes of the medical officers concerned, for his first clinical sign was a rise in pulse only half an hour before being examined and his rapid deterioration noted.—I am, etc.,

Malvern, Worcs. JOHN C. A. RAISON.

SIR,—Like your correspondents, I found Sir James Learmonth's paper on "Surgery of the Spleen" (July 14, p. 67) of great interest, particularly since I have had to deal with traumatic rupture of the normal spleen on five occasions.

The first case was a boy of 16, who was thrown violently over his bicycle handlebars.

The second was one of multiple injuries following a road accident.

The other three cases have been of special interest because of their common aetiology. They have occurred in steelworkers, and I will give the typical history of the most recent case.

These men work one of three shifts in the 24 hours; the work is hot, and they require a heavy overcoat on leaving work, which in time shrinks and becomes tight-fitting. They also wear heavy iron-studded and iron-toed boots. The mid-shift meal of sandwiches is carried in a "bait box"—a tin box 7 in. by 5 in. by 3 in.—and tea in an enamel can with handle. One man, aged 39, a plater's helper, had finished his shift and had buttoned up his coat to the neck. His left hand was in his pocket and his box wedged between his left arm and his side, opposite the lower left ribs. His right hand was through the handle of the can and in his right side-pocket. While walking over concrete he slipped and fell on his left side, his anchored hands being unable to break his fall, and he was taken to the ambulance room with severe pain in the region of the lower left ribs. Strapping was applied and he was referred to hospital. I saw him about two hours after the accident, when he was very shocked, with rigid abdomen, and tender in the left hypochondrium. He had no shoulder pain. Blood pressure 80/50 mm. Hg, pulse 140/min. After blood transfusion the spleen, which was of normal dimensions and mobility but had a transverse tear of substance and pedicle, was removed by a left paramedian incision. He made an uneventful recovery. He had no fractured ribs.

One of the other cases had the force applied similarly, but demonstrated the "latent period" mentioned by McIndoe, which in his case lasted about 12 hours.

From my experience, therefore, it would appear that it is the local application of considerable force causing acute lateral flexion of the trunk and consequent squeezing of the spleen against the vertebrae which causes the rupture.—I am, etc.,

Middlesbrough. G. E. FORDYCE.

Treatment of Migraine

SIR,—With regard to your annotation on migraine (September 1, p. 538) and the correspondence arising out of it (September 15, p. 673), I am extremely interested in this condition and its prophylaxis, and am at present carrying out a detailed analysis of some 40 cases in my own practice. The criteria for diagnosis which I use are those of aura, unilateral headache of varying intensity, accompanied by or terminating with vomiting or dyspepsia. All my cases have been refracted for any minor error, and I have been agreeably surprised by the lessening in frequency of attacks in some of those who have not only had their refractive errors corrected but have been given tinted (Crookes A) lenses.

The drug of choice which has given excellent results for those with frequent attacks has been phenobarbitone given usually in the early evening in doses of ½–1 gr. (32–64 mg.). In at least 50% of cases the attacks have ceased altogether, while in the remainder the attacks are considerably lessened in intensity and frequency.

I have also found it possible to reduce the dose of phenobarbitone in those without attacks for twelve months, and in some to wean them of it altogether. It is too early to say yet whether this latter group will have recurrences and, if so, after how long.

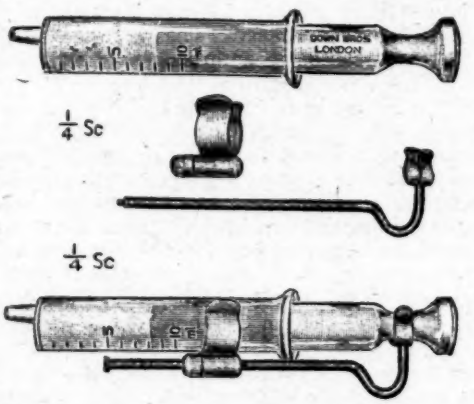
In those cases associated with the menses, it is possible to use the drug during the period alone, with an overlap of a few days on either side. This is not so in every case, however.

I have no doubt that mental worry or stress, or, in the case of women, changes in temperament associated with the approach of the menses, are definite "trigger" factors in those persons predisposed to migraine, hence the rationale of the treatment suggested.—I am, etc.,

London, W.4. M. D. CAPLAN.

Piston Check for All-glass Syringes

SIR,—One of the minor inconveniences of all-glass syringes is the liability of the plunger to come completely away from the barrel, either while drugs are being prepared, or when the syringe is lying on a table. British Standard 1263:1946 for hypodermic syringes 4.C(V) states that "a brake for the piston shall be provided. . . ." These brakes, however, do not prevent the plunger from coming away



from the syringe. The piston check illustrated has been made by Messrs. Down Bros., of 92/94, Borough High Street, London, S.E.1. It is supplied in three sizes to fit 5-, 10-, and 20-ml. syringes respectively, and effectively prevents the plunger from being accidentally pulled out of the barrel. It may either be fitted to a syringe immediately before use, or, if preferred, syringe and piston check may be autoclaved together.—I am, etc.,

London, S.E.1. T. H. S. BURNS.

Indian Remedies for Poor Memory

SIR,—Regarding a reply in "Any Questions" (August 11, p. 372) on treating impairment of memory, I have two suggestions to offer, which may be verified by tests on experimental animals and by clinical trials. The first is a well-known drug of the indigenous Indian Ayurvedic medical system, which has given very favourable results in a large number of cases of juvenile feeblemindedness, impairment of memory, and deterioration of general mental function.

The seeds of a large climber found in the mountain regions of India, *Celastrus paniculata Willd.* (family *Celastraceae*), called jyotish-mati (Sanskrit), malkangani (Hindi), etc., are crushed and administered with aromatic drugs in capsules in doses of 3 gr. gradually increased to 10 (0.2 to 0.65 g.), given twice daily with milk for eight to twelve weeks. Alternatively the seed-oil can be administered in doses of 5 to 10 minims (0.3 to 0.6 ml.), twice daily. Two alkaloids, celastrine and paniculatine, have been found in the seeds, and it is remarkable that the leaf-juice is used as an antidote for opium poisoning, while a very closely allied species of gymnosporia is used in Africa for epilepsy and madness.

From the same botanical family comes the suggestive *Catha edulis Forsk* (*Methyscophyllum glaucum E. and Z.*), a well-known and excellent African stimulant beverage called "bushman's tea," also containing celastrine, along with other alkaloids, and having propadrine-caffeine-amphetamine-like actions, stimulating the central nervous system without subsequent secondary depression.

Another valuable drug, similarly administered, is the powder of the seeds of *Lawsonia inermis Linn.* (*L. alba Lam.*) (family *Lathraceae*), known as henna (English), mendi (Hindi), etc., which has a slower cerebral stimulant action.

I have clinical records covering over 100 years of a continuous family medical practice, wherein these two drugs have been used with very favourable results.

A few references are given below.—I am, etc.,

Oxford. SOHRAB A. E. HAKIM.

REFERENCES

Basu, M. K., and Pabrai, P. R. (1946). *J. Amer. Pharm. Ass.*, **35**, 272.

Dymock, W., Warden, C. J. H., and Hooper, D. (1890). *Pharmacographia Indica*, **1**, 343; **2**, 41. London.

Kirtikar, K. R. (1933). *Indian Medicinal Plants*, **1**, 574; **2**, 1077. Allahabad.

Solanki, Nargund, and Kanga (1929). 16th Indian Science Congress, Madras.

The Dispensatory of the United States of America, 24th edition, 1947, pp. 1389, 1390, 1502, 1620. Philadelphia.

Watt, G. (1889). *A Dictionary of the Economic Products of India*, **2**, 237; **4**, 600. Calcutta.

Watt, J. M., and Breyer-Brandwijk, M. G. (1932). *The Medicinal and Poisonous Plants of Southern Africa*, p. 110. Edinburgh.

Resistance to Disease

SIR,—Dr. L. E. Houghton (September 8, p. 609) quotes a statement from an American medical research committee who are concerned about "the action of A.C.T.H. and cortisone on the factors of resistance to tuberculosis."

Metchnikoff discovered purpose in the inflammatory reaction. The cellular exudate resists the infection. The tubercle resists the tubercle bacilli which it contains. But the tubercle is also the anatomical basis of tuberculosis. Within itself it equates resistance with disease. Therefore, if the body resists tuberculosis it resists its own resistance. It has occurred to me, of course, that "resistance to disease" is only a loose and careless way of writing resistance to infection. Metchnikoff in his writing frequently confuses infection with disease. But the late Wilfred Trotter was not a careless writer, and I find the phrase occurs frequently in his essays. Writers of modern textbooks of immunology fall back on the phrase when trying to explain how increase in resistance can effect a decrease in the amount of lesion. It is a stock phrase used by many authors to provide at least a teleological explanation of the therapeutic effects of A.C.T.H. and cortisone. It should be noted, of course, that, while you might increase the "resistance to disease" in rheumatism or psoriasis, you cannot very well influence the "resistance to infection" because as yet there is no infection to be resisted. The fact is that writers of all kinds of modern textbooks and contributors to medical journals find the phrase almost indispensable. A recent contributor to the *Journal* wrote of defence against mental disease. There is an ancient animistic concept in which disease was a demon which could possess its victims. This would fit in with the attack-and-defence analogy, but I can hardly believe that modern scientific writers have this concept in mind. But if not a demon, what in, say, schizophrenia is there to be resisted?

The attack-and-defence analogy is good enough to explain many of the phenomena of disease, including the essential weakness of rigorous defence. In disease Metchnikoff could have recognized many parallels to the suicidal defence of Moscow in 1812 just as we can recognize the counterparts of the "scorched earth" defence reactions of this century. So long as we can identify infection it is rational to speak of resistance. When no infection can be recognized the analogy is not to be taken too seriously. Finally, if the analogy has any value at all it makes "resistance to disease" irrational. Either disease has reference to concrete things such as the lesion which embodies most of the "resistance," or it is an abstraction—a label describing a category of phenomena. In either case it is not to be resisted.

Your "Refresher Course" of articles opened a window on the current teaching of the "principles" of medicine. Foremost among the principles was "resistance to disease." I cannot think why an expression which I once found satisfying should now irritate me, and I do admit that "resistance to disease" does irritate me. Perhaps it is because "aggression," "defence," and "resistance" have lost their serious significance in this age of militant pacifism. To give up the whole idea of resistance as the basis of inflammation would, I suppose, be too much to ask. A universe without purpose, a little world without end inside the lesion, would be an unattractive substitute for Metchnikoff's hypothesis. The hypothesis has been useful when we wanted to classify a large group of disease reactions under the heading of defence reactions or resistance. I still consider the classification or grouping valid, but could anybody suggest how we can preserve the classification and at the same time avoid irrational "resistance to disease"?—I am, etc.,

Bristol. WILLIAM HUGHES.

Clinical Directives in the R.A.F.

SIR,—It may not be generally known that in the R.A.F. a station medical officer is directed how he shall or shall not treat various maladies. For example, any patient with a condition of the eye, ear, nose, or throat which is deemed to require a course of penicillin must first be seen by the hospital specialist before such treatment can be sanctioned. There are certain provisos concerning the treatment of boils and carbuncles, one rather curious proviso being that penicillin is "forbidden" as a substitute for surgery but may be used as an adjunct to surgery. The local application of sulphonamide powder is forbidden altogether except on specialist advice.

During the last 12 months there has been an increase in directives containing instructions of this type flowing from the Air Ministry to its medical officers. It would appear that the Air Ministry is taking a hand in the treatment of individual patients through the medium of orders to its M.O.s. This can do nothing but harm. It is an attempt to standardize beyond any reasonable degree medical practice in the R.A.F. Every patient with his illness is a law unto himself in the nature of his reaction to disease and his response to treatment. In order to serve his patient best a doctor must be able to exercise his judgment in each individual case with no restraints; he should not have to consider what is or is not permitted. Nor should he be required to have the sanction of a specialist in certain cases—for example, acute otitis media—before giving treatment.

For what reason does the Air Ministry give such orders, which sometimes seem to amount to a denial of one's medical degree? Is it to produce better medical attention for R.A.F. personnel? Does it arise from a fear of compensation claims and disability pensions which might arise from illness? Or is it lack of trust in its medical officers and doubt of their competence? Surely the motive lies in this last, the first two being corollaries of this. Should this be correct, it is plainly undesirable to continue to employ doctors the competence of some of whom, at any rate, is doubted.

It is true to say that the R.A.F. medical branch is administered by the regulars, but the largest part of medical practice is carried out by National Service doctors. Perhaps here lies the Air Ministry's lack of faith, and lacking faith it is nevertheless compelled to engage such men due to shortage of medical man-power. If this underlies the policy, it is unjust and, moreover, founded on false premises.

There are a number of unfavourable working conditions in the Services. For example, there is no free choice of patient for doctor or doctor for patient, which can indeed be most irksome and give rise to unpleasantness where families are concerned, but it is inseparable from Service life and therefore must be accepted. However, the encroachment by the Air Ministry hierarchy on one's professional liberty as a doctor is avoidable, unnecessary, and thoughtless. It is difficult to imagine a doctor worth his salt obeying such directives when his clinical judgment dictated otherwise, or regarding them with a respect one would like to give, coming as they do from such an august organization.

That this letter may not be entirely without constructive effort, I suggest that perhaps the information could be imparted in the form of recommendations, not commands, when they would no longer be so exceptionable—but not necessarily acceptable.—I am, etc.,

Medical Officer.

Injuries in Flying

Sir,—I have read with particular interest Dr. Donald Teare's article on "Post-mortem Examinations on Air-crash Victims" (September 22, p. 707), and appreciate his contribution to necropsy procedure. Certain facts relating to the accident he discusses, and the conclusions that he has drawn, would appear to have escaped his consideration, however.

The Viking aircraft in question is designed to carry 27 passengers. It has six "backward-facing seats"—three with their backs to the main-spar, the most rigid and indestructible portion of the aircraft, and three with their backs towards the main forward bulkhead. There were 26 passengers on board this particular flight, which means that *at least five passengers were sitting in aft-facing seats.* Since the normal trim loading of an aircraft at time of take-off or landing requires that, in the absence of a full complement of passengers, the rear seats shall be left vacant, it can be assumed that on this occasion *all six aft-facing seats were occupied. All the occupants died from injuries,* while the only passengers and stewards surviving in this and the Mill Hill Dakota accident were sitting in *forward-facing seats—wearing lapstraps.*

Investigation of the Viking accident shows that the main impact occurred when the starboard wing struck the runway at some 80 to 90 knots and was severed from the main part of the aircraft. After this the aircraft slewed round some 80 degrees before coming abruptly to rest against a heap of iron pipes. In such an incident the force and line of the deceleration would not be truly forward but at some degree towards the lateral aspect of the passengers. Under these conditions the arm-rests of the chairs, being higher and more rigid than the lapstraps, were probably responsible for some of the intra-thoracic, liver, and spleen injuries which Dr. Teare attributes to the lapstraps (which incidentally come over the groin and lower part of the abdomen or upper thigh). Radio officers, because of their operating stations in the aircraft, normally sit at an angle of some 45 degrees to the line of the fuselage. This might account for the similarity of injuries (i.e., ruptured aorta), to which Dr. Teare refers in the case of the radio officer in this accident and the radio officer in the Dakota accident. (Incidentally, in the latter case the victim suffered a rupture of the *ascending* portion of the aorta and not the descending as Dr. Teare's article implies.) Axial torsion of the body with lateral flexion would appear to play an important part in the causation of these ruptures of the aorta, and in some instances of the injuries sustained by the liver and spleen.

In the case of the Mill Hill (Dakota) accident all passenger seats were forward-facing. In the opinion of the three well-known pathologists (of whom Dr. Teare was one) who performed these necropsies, only three of the 28 deaths were *primarily* due to fractures of the skull, and of these two were members of the operating crew, the pilot and co-pilot, both of whom had other multiple injuries: unfortunately it is not yet possible for operating members of aircrew, such as pilots and co-pilots, to sit facing aft.

It would have been valuable if fuller details of the sites of the fractures of the skulls had been given. Some of these may have been sustained by the victim having been struck by an article spilling from the luggage rack. Even a lady's small rigid travelling or make-up case with sharp corners becomes a missile with lethal potentialities under such severe forces of deceleration—particularly if the target victim is rigidly supported by the main-spar of the aircraft.

The theoretical value of aft-facing seats is not in dispute, but, unless seats, their anchorages, and certain floor structures are stressed to considerably higher values than that at present required by the controlling authorities, there is little safety potential to be gained from a "right-about-turn" of the seats alone. B.O.A.C. and B.E.A. have been actively engaged in researches on all aspects of this subject for the past three years—including the views of the travelling public. Accident statistics if unrelated to all relevant factors can be very misleading. While fully appreciating Dr. Teare's comments, I would suggest that an accurate deduction of the cause of such injuries (as portrayed by post-mortem findings alone) can be made only after relating their nature to *all* the factors and forces—particularly their value and direction—ensuing at the time of the accident. Having visited the scenes of the accidents in question within an hour of their happening, seen the victims, and sat as a member on the Corporation's Accident Inquiry Committee, I marvel that any living being, however seated, could have escaped from such total destruction.—I am, etc.,

A. Buchanan Barbour,
Chief Medical Officer.

British European Airways.

Herpes Zoster Involving Anterior Horn Cells

Sir,—The article by Dr. J. H. McIntyre (September 22, p. 716) induces me to report a similar case which occurred 18 months ago.

A woman, single and living alone, aged about 38, contracted a severe herpes zoster in the distribution of the mandibular division of the fifth cranial nerve. She was treated with three injections of 4 ml. of a comprehensive liver extract given intramuscularly three days apart, a treatment which has proved very effective in my experience in about nine cases out of ten—this unfortunately was the tenth. The rash and pain were beginning to subside, about four weeks after she was first seen, when she developed a typical Bell's palsy, which persisted for six months before all traces of facial asymmetry disappeared. There was no upset of hearing or taste, nor was dryness of mouth complained of.

I had ascribed the palsy to local causes—e.g., irritation at site of exit from stylomastoid foramen of the seventh nerve by either skin eruption or frequent local applications—but the above-mentioned article has made me consider whether there has been a closer relationship—e.g., spread of virus from fifth nerve to the facial ganglion.—I am, etc.,

J. F. H. Wood.

Glasgow.

Diathermy and Television

Sir,—Television test transmissions from the new Holme Moss station in the North of England have indicated a widespread interference by electro-medical equipment, which operates on a frequency near that used for television transmissions. Apart from hospitals, it has been suggested that private practitioners may be using equipment which is causing interference.

This problem formerly arose, although to a lesser extent, in the South and Midlands, where it was overcome by manufacturers carrying out modifications to equipment. There are two ways of overcoming the problem. The first is by "screening" (surrounding with wire mesh), as fully explained in the G.P.O. pamphlet *Radio Interference C.2201,* which is free on application. A second method is to alter the frequency on which the medical equipment operates; this can be done without impairing its curative efficiency. The G.P.O. is approaching manufacturers to ask them to make all future equipment on frequencies outside the television band; and for existing equipment, manufacturers are prepared to co-operate by supplying the parts required to make the necessary alterations, which can be carried out by their agents or by a suitably qualified engineer.

Sooner or later all cases of reported interference are investigated by the G.P.O., but in the case of diathermy interference they have indicated their willingness to advise on preventive measures before a complaint is lodged. May we therefore ask all users of electro-medical equipment to co-operate by asking their local telephone manager for an engineer to inspect their equipment?—I am, etc.,

S. E. Allchurch,
Secretary.

British Radio Equipment Manufacturers' Association.

Obituary

P. G. McEVEDY, F.R.C.S.

Mr. P. G. McEvedy, senior surgeon at Ancoats Hospital, Manchester, died at his home at Bucklow Hill in Cheshire on September 21. He was 61 years of age.

Peter George McEvedy was born at Blackwater, Christchurch, New Zealand. He went to school in Christchurch and then came to this country to study medicine at Guy's Hospital, where he won many of the prizes open to students. After qualifying in 1916, he worked as Arbuthnot Lane's house-surgeon before joining the New Zealand Medical Corps, in which he served in France and with the Army of Occupation in Cologne. On demobilization he returned to further study in London, taking the F.R.C.S. in 1920 and graduating M.B., B.S.(London) in the same year. He then moved north to Oldham, where he was in general practice for a short time before becoming resident surgical officer at Ancoats Hospital, Manchester. After a year in that post he was appointed to the staff of the hospital as assistant surgeon. His ability and personality were such that he was soon in the first flight of Manchester surgeons. Besides his appointment at Ancoats he was also on the staff of the Warrington Infirmary and Stretford Memorial Hospital. Last year the Manchester Medical Society paid him the honour of electing him its president.

We are indebted to Sir Heneage Ogilvie for the following appreciation: Peter McEvedy was one of the founders of the Surgical Travellers Club in 1927, and in the quarter of a century he never missed a meeting. He was in Copenhagen at Whitsun, as charming and energetic as ever, and looking better than usual. He did his last operation before the Association of Surgeons in July.

McEvedy held an almost unique position in surgery. He was the best operator that Guy's has produced, and possibly the best operator in the world. I make this statement soberly, having in mind to-day's leaders in many countries and such giants of the immediate past as Kirschner, Wilkie, and Moynihan. His gastric work attained a perfection that I have never seen equalled by anybody. His thyroid operations, done almost entirely with the knife, were just so much better than the work of the best thyroid surgeons in England and America that they left the spectator with a sense of frustrated humility; here was a standard that no ordinary man could attain. He was sure, he was deft, he was gentle, he was bloodless.

His example did much to rehabilitate the Billroth I gastrectomy within recent years. His operation for femoral hernia, published in the *Annals of the Royal College of Surgeons*, has replaced all others in the hands of those who have once tried it. He was, however, much more than an operator, and it was impossible to spend a few hours in his company without absorbing some of his philosophy, without learning a great deal of value. He was perhaps at his best as a postgraduate teacher and an instructor of young surgeons.

Peter McEvedy was never as widely known as he should have been. He was gentle and truly humble. Though he had much to say and could say it well, he wrote little and seldom spoke in public. His poor health kept him from social functions, but he found happiness in his home life and in the company of his friends. To his pupils and those who knew his work he had no equal.

Dr. Philip Halbert Green died at his home in Portsmouth on August 22, aged 73. He was one of the city's best-loved family doctors and was associated with the work of the Portsmouth and Southern Counties Eye and Ear Hospital for nearly 40 years. After graduating M.B., Ch.B. at Manchester in 1901 Dr. Green obtained a resident post as house-surgeon at the Royal Infirmary. He then spent a year in the Far East as a ship surgeon. In 1905 he moved to Portsmouth and joined his father's practice. His two younger brothers—the late Drs. Stephen and John Green—also entered the partnership. Philip Green was appointed honorary anaesthetist to the Eye and Ear Hospital in 1907, assistant surgeon in 1922, and surgeon in 1928. From 1941 until his retirement from the staff in 1944 he was senior ear, nose, and throat surgeon. In recognition of his long service to the hospital he was made an honorary consulting surgeon. During the first world war Green served in the R.A.M.C., and was taken prisoner at Bapaume in March, 1918. In the last war he was the hero of one of Portsmouth's heaviest air-raids (on August 12, 1940). Bombs exploded only a few yards away just after he had started a mastoid operation at the Eye and Ear Hospital, but despite the constant noise and vibration he carried on his task for half an hour until the operation was safely completed. Then, after he had carried the patient, a 5-year-old boy, to shelter, he assisted in salvage work at the nurses' wing, which had been set on fire. Soon afterwards the Portsmouth and District Friendly Societies' Council, acting for the city's 50,000 friendly-society members, passed a resolution expressing appreciation of Dr. Green's "courageous action." For a brief period in the nineteen-twenties Dr. Green served on the city council as a representative of Charles Dickens Ward. He was a loyal and enthusiastic supporter of the B.M.A., and in 1928–9 he was chairman of the Portsmouth Division. A professional colleague said of him: "His 37 years on the hospital staff is a marvellous record of service, especially in view of the fact that during the whole of that time he was also conducting a very busy general practice. He was particularly well loved by the poor of Old Portsmouth and district, for whom he did wonderful service as a family doctor."

The death of Dr. Henry James Bumsted on August 30 brings to a close a long and useful medical career of an unusual nature. A man of singular charm, gentleness, and courtesy, he was born into very comfortable circumstances in 1868, and was educated at Dulwich College and at St. John's College, Cambridge, receiving his clinical training at St. Bartholomew's Hospital. He graduated B.A. in 1890, with second-class honours in Part I of the natural sciences tripos, and qualified M.R.C.S., L.R.C.P. in 1896. In the following year he proceeded M.A. and took the degrees of M.B., B.Chir. Following an appointment as house-surgeon at Barnsley in 1888, he then, in accordance with a strong principle, spent the rest of his active life in unpaid medical work. This was a matter of great concern to him, that his medical work should never deprive a colleague of a salary, however small. For 25 years he served the Billingsgate Christian Mission in an unpaid medical capacity, and during the war of 1914–18 he gave his services to the Volunteer Training Corps as lecturer and such other duties as were required. He worked for many other charities, serving the Royal Blind Pension Society, Cambridge University Mission, Bermondsey, Herschell's Homes, Camberwell, and the British and Foreign Bible Society for 50 years. A gifted musician, he was president of the Cambridge Musical Society in his time, and music remained a delight all his life. Long residence in Streatham strengthened an early admiration for Dr. Johnson, and he had a profound knowledge of the life, works, and times of Boswell's hero. All his life a devout Christian, his later years were occupied in duties in his local church, and this, combined with a happy home and spacious garden, gave him a serene contentment which he seemed to be able to radiate to all who were so glad to be associated with him.

Dr. RAY A. PATELSKI, well known for his work on synthetic vitamins and antibiotics, died on September 7 in New York after a short illness. He was 45 years of age. Educated at the University of Michigan, he took the degrees of B.Sc. (Pharmacy) in 1927, M.Sc. in 1933, and Ph.D. (in organic chemistry) in 1936. From 1927 to 1938 Dr. Patelski held a number of university appointments, and he then joined the chemical research department of Chas. Pfizer and Co. Inc. At the time of his death he was co-ordinator of clinical investigations. In the latter phase of his career he became well known to physicians in many parts of the world. During the second world war he served in a civilian capacity with the Office of Scientific Research and Development of the National Research Council (U.S.).

Dr. GEORGE DE SWIET, chairman of the Paddington Division of the British Medical Association, died suddenly on September 23, aged 68. He had been in practice in Paddington for over 30 years. A Pole by birth (he changed his name after settling in this country), he studied medicine at a number of the most famous medical schools in Europe and graduated M.D. at Munich in 1910. After coming to this country and studying at the London and King's College Hospitals he took the Conjoint qualification in 1912. During the first world war he was a civil medical officer to the 4th London General Hospital, Denmark Hill. After settling in Paddington he took a keen interest in political as well as medical affairs. In fact, at the General Election in 1935 he stood unsuccessfully as the Liberal candidate for Paddington North. An active member of the British Medical Association, he acted as the representative of the Paddington Division from 1938 to 1951 without a break, and from 1944 until the time of his death he was chairman of the Division. A post to which he brought his special knowledge and qualifications was the honorary presidency of the Polish Medical Association in the British Empire. Besides publishing a number of letters in this *Journal* on medico-political subjects, he was the author of a book entitled *Mechano-Therapeutics in General Practice* (published in 1914), and he translated Rollier's *Heliotherapy of Tuberculosis.*

Dr. G. M. Gray writes: We in Paddington are very conscious of the loss of our chairman, Dr. George de Swiet. The Paddington Division was largely created by him, when he thought the Hammersmith and Kensington Division was somewhat too circumscribed for all the various opinions in the area. We could always count on a warm breath of salutary radicalism at our meetings, and sometimes what was thought to be a voice in the wilderness proved at a later date to be the considered opinion of earlier critics. There was never any venom, but a spade was a spade and should be so called. While much interested in medicine, and especially in all advances that would help his patients, he had a much wider horizon, and the betterment of mankind, as well as the individual, held his interest and led him into the medico-political world. He had been a member of the London County Council, the Paddington Borough Council, and the Insurance Acts Committees of London for many years. His charm of manner endeared him to many who may not have shared his views. All of us will miss his kindly presence and enthusiasm and mourn him as a most happy friend. Our sympathy goes out to his wife and son, who, as a medical consultant in Wales, is carrying on his father's tradition of service.

The discovery of a plot to export about 80 lb. of streptomycin to Spain led to the arrest of 50 people in Lisbon (*Le Figaro*, September 24). The distribution of the drug in Portugal is solely the responsibility of the Red Cross, and the stolen goods were said to have been obtained through the complicity of several employees, and also by means of faked prescriptions.

Medico-Legal

A.I. AND THE JURISTS

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

It has always been the proud boast of English lawyers that the unwritten Common Law of England, expounded but not made by the judges, and to be found not in any written code but in the judges' bosoms and in the reports of their judgments, is flexible enough to meet the substantial changes which have taken place in the everyday life of England since Norman times. One of these changes, a change in what has been one of the lawyers' basic assumptions—namely, that the birth of a child presupposed sexual intercourse between a man and a woman—has been brought about by the growth of the practice of human artificial insemination. The kind of problem this has raised in the English law of nullity of marriage, and how the judges have solved it, was the subject of a report in these columns last week.

Similar problems are now exercising the jurists of Scandinavia, who do not enjoy the English common law. A judicial commission representing the four Scandinavian countries has been specially appointed at the instance of the Danish Minister of Justice to consider them. Two problems in particular are to be submitted to the commission.

A woman during her marriage to Mr. A had a child by artificial insemination without medical supervision by a donor named Mr. B, whose identity she knew. Her marriage to Mr. A was later dissolved, and she married Mr. B. Mr. A and Mr. B each claim the custody of the child on the ground of being its father. Secondly, there is a proposal that unmarried women should in special circumstances be officially allowed to have children by A.I.

The answer to these two problems in English law would undoubtedly be this: if it was proved that the child was born as a result of Mr. B's intervention by artificial insemination and could not have been born as a result of normal intercourse with Mr. A, Mr. B would be found to be an adulterer and father of the child. The single woman could bring successful bastardy proceedings against the artificial-insemination donor, if she could identify him, as putative father of the child.

The answer of the Scandinavian judicial commission has yet to be given.

Universities and Colleges

UNIVERSITY OF OXFORD

The University is proposing to offer one scholarship, renewable annually, to a medical student of high academic distinction wishing to take his clinical course at Oxford. The scholar will be free to take the final medical examinations of his own university or, provided he is eligible, the Oxford B.M. degree. The scholarship will be awarded on interview and record and will be of an approximate value of £250 a year for three to five years according to circumstances. It will not be available to enable a student to undertake research and it will cease on medical qualification. Full particulars and application forms may be obtained from the secretary of the Medical School, University Museum, Oxford.

UNIVERSITY OF LONDON

Professor J. M. Mackintosh will deliver the Heath Clark Lectures on "Trends of Opinion about the Public Health, 1901–1951" at the London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., on November 6, 8, 13, 15, and 19, at 5 p.m. The lectures are addressed to students of the University and to others interested in the subject. Admission is free, without ticket.

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles for the week ending September 15 (No. 37).

Figures of notified *cases* are for: (*a*) England and Wales (London included). (*b*) London (administrative county). (*c*) Scotland. (*d*) Northern Ireland. (*e*) Eire. Figures of *births and deaths* and of *deaths* recorded under each disease are for: (*a*) The 126 great towns in England and Wales (London included). (*b*) London (administrative county). (*c*) The 16 principal towns in Scotland. (*d*) The 10 principal towns in Northern Ireland. (*e*) The 13 principal towns in Eire. A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, Northern Ireland, and Eire, the Ministry of Health and Local Government of Northern Ireland, and the Department of Health of Eire.

Disease	1951 Week Ending September 15					1950 Corresponding Week					1942–50 England & Wales Corresponding Week		
	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	Highest	Median	Lowest
Diphtheria	36	2	13	—	1	37	6	10	3	2	875	255	38
Deaths	—	—	—	—	—	—	—	—	—	—			
Dysentery	103	28	82	—		215	10	94	—	1	351	184	50
Deaths		—		—			2		—				
Encephalitis, acute	4	—	—	—		11	1	1	—	1	11	1	—
Deaths		—			—		—			—			
Erysipelas			12	1	4			21	2	8			
Food-poisoning	166	15		3		180	47		1				
Infective enteritis or diarrhoea under 2 years				12	43				13	28			
Deaths	8		2	1	2	12		3	1	2			
Measles*	1,211	35	78	101	34	2,494	146	80	45	35	2,998	1,155	497
Deaths		—	—	—	—		—	2	—	—			
Meningococcal infection	23	2	10	—	1	28	4	13	—	2	73	34	25
Deaths		1	1				—	—					
Ophthalmia neonatorum	35	2	7	—	1	52	9	7	—		93	71	47
Pneumonia, influenzal	212	9	1	3		218	14	1	1		402	284	203
Deaths (from influenza)†	2	—	1	—	—	1	—	—	—	—			
Pneumonia, primary			122					128					
Deaths	109	18		7	5	108	11		4	6			
Poliomyelitis, acute:													
Paralytic	42	6	12	7	2	478	29	77	24	3	614	33	16
Non-paralytic	48	5											
Deaths§	—	—			—	23	2			—			
Puerperal fever			7					6					
Puerperal pyrexia‖	263	32	12	—		87	7	8	—		198	124	87
Scarlet fever	595	43	145	23	45	750	49	148	47	51	2,654	925	674
Deaths		1	—	—	—		—	—	—	—			
Smallpox	—	—	—	—		—	—	—	—				
Deaths				—					—				
(1) Tuberculosis, respiratory			126	28				171	16				
(2) Tuberculosis, non-respiratory			23	4				32	7				
(1) Deaths	119	13	18	3	5	125	11	17	3	11			
(2) Deaths		3	6	2	3		4	4	—	2			
Typhoid fever	10	1	2	—	1	8	2	3	—	2			
Deaths¶	—	—	—	—		1	—	—	—		50	22	13
Paratyphoid fever	38	4	—	1	1(A)	11	1	—	—				
Whooping-cough	2,420	112	305	43	89	3,086	267	186	19	65	3,086	1,519	1,083
Deaths	3	—	—	—	—	8	2	—	—	1			
Deaths (0–1 year)	201	24	24	8	9	193	24	31	8	16	360	316	193
Deaths (excluding stillbirths)	3,901	618	484	91	134	4,074	627	492	105	158	4,074	3,793	3,422
Annual death rate (per 1,000 persons living)			9·9					9·9					
Live births	6,524	1,110	745	188	390	6,602	1,056	828	213	431	8,953	6,602	5,861
Annual rate per 1,000 persons living			15·3					16·6					
Stillbirths	166	22	14			179	21	23			243	203	179
Rate per 1,000 total births (including stillborn)			18					27					

* Measles not notifiable in Scotland and returns are approximate. † Includes primary form for England and Wales, London, and N. Ireland. § The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, and London (administrative county), are combined. ‖ Includes puerperal fever for England and Wales and for Eire. ¶ Deaths from paratyphoid fever are combined with those from typhoid fever.

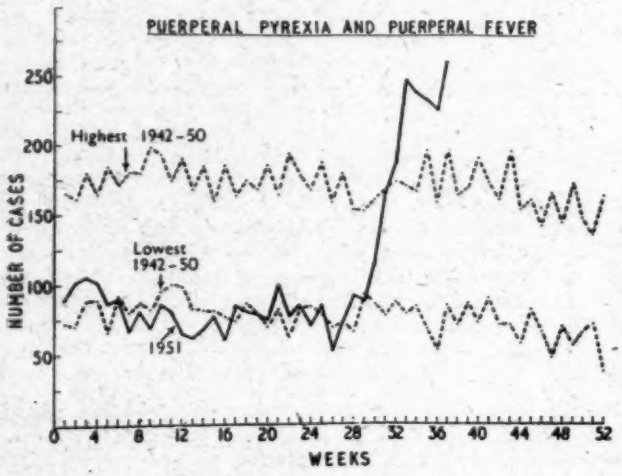
Vital Statistics

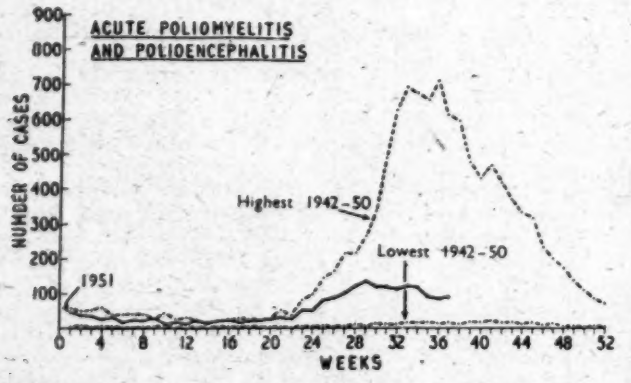
Poliomyelitis

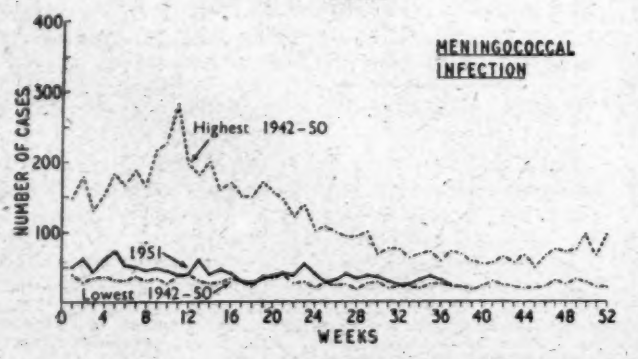
Poliomyelitis notifications in the week ending September 22 were as follows (figures for the previous week in parentheses): paralytic, 48 (42); non-paralytic, 37 (48); total, 85 (90). There was a further drop in the percentage of non-paralytic cases to 43.5%, and the tendency of recent weeks to a decrease to more normal proportions of this type of the disease was maintained. The overall incidence of the disease in England and Wales to date is 4.77 per 100,000.

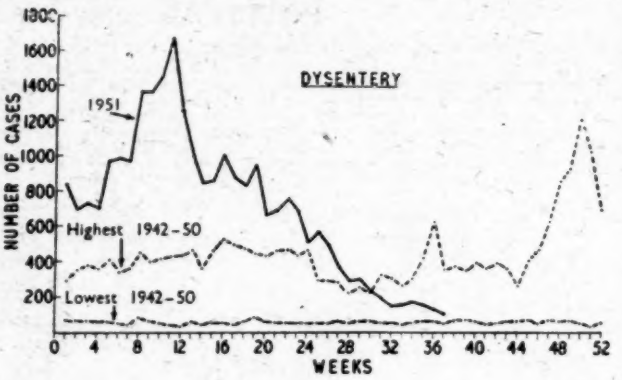
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported during the nine years 1942–50 are shown thus ------, the figures for 1951 thus ————. Except for the curves showing notifications in 1951, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

During the week ending September 15 in England and Wales a fall occurred in the number of notifications of measles 176, whooping-cough 156, and dysentery 28, while the only rise of any size was scarlet fever 96.

The largest fluctuation in the local returns of measles was a decrease of 63 in Lancashire. Only small variations were reported in the incidence of scarlet fever. The largest decreases in the number of notifications of whooping-cough were 38 in Staffordshire and in Warwickshire. The notifications of diphtheria were 4 fewer than in the preceding week; the largest change in the local returns was a decrease of 4 in Staffordshire.

An increase of 6 was reported in the number of notifications of paratyphoid fever; 9 of the 38 cases were notified in Lancashire. An increase of 6 also occurred in the notifications of typhoid fever. The 10 cases were contributed by 9 counties.

The notifications of acute poliomyelitis were 4 more than in the preceding week. The paralytic cases decreased by 5, while the non-paralytic cases rose by 9. The largest centres of infection during the week were London 11 (scattered through nine boroughs), Yorkshire West Riding 10, Lancashire 7, and Kent 5.

The largest of the fresh outbreaks of dysentery notified during the week was Cornwall, Helston M.B. 8. The largest returns were London 28, involving 15 boroughs, Middlesex 11, and Lancashire 10.

New Zealand Infant Mortality

In 1950 the infant mortality rate per 1,000 live births in New Zealand was 22.7 for people of European stock and 69.7 for Maoris (*New Zealand Monthly Abstract of Statistics*, July, 1951). The comparable figure for England and Wales was 29.8.

Worst Month for Road Accidents

July was the worst month for road casualties since the war, reports the Ministry of Transport. These totalled 21,811 as compared with 21,044 in July last year and with 22,684 in July, 1939. Deaths numbered 440, seriously injured 5,202, and slightly injured 16,169. More than 70% of the increase of 767 in total casualties above July, 1950, arose from accidents on Sundays, when there is more pleasure-travel than on any other day of the week. A regrettable feature of the July figures is the increase in the number of child pedestrians killed—69 compared with 56 in July, 1950.

Week Ending September 22

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 621, whooping-cough 2,196, diphtheria 31, measles 1,069, acute pneumonia 281, acute poliomyelitis 85, dysentery 107, paratyphoid fever 28, and typhoid fever 10.

Medical News

General Election Manifestos

Little has so far been said about the Health Service by the two political parties which have issued election manifestos. The first to appear was the Conservative manifesto. This states that "in education and in health some of the most crying needs are not being met. For the money now being spent we will provide better services, and so fulfil the high hopes we all held when we planned the improvements during the war." The manifesto adds that the care and comfort of the elderly is a sacred trust. The next manifesto to appear was the Labour Party's. This states that in the inter-war years "dread of doctors' bills was a nightmare in countless homes, so that good health cost more than most people could afford to pay. Now we have a National Health Scheme which is the admiration of the post-war world." Later on the manifesto says that the Conservatives "have voted in Parliament against the National Health Service," and, finally, "Never have the old folks been better cared for. Never had we so happy and healthy a young generation as we see in Britain to-day." The Liberal and Communist Parties had not issued their manifestos before we went to press.

Annual Dinner of the Royal College of Obstetricians and Gynaecologists

Fellows and Members of the Royal College of Obstetricians and Gynaecologists with their guests formed a large company at the annual dinner of the College, held at the Dorchester Hotel on September 28. Among the guests were the Minister of Health, the Ambassador of Eire, the Governor-General of Australia, the High Commissioners of Australia and India, and many men and women distinguished in medicine and other walks of life. Mr. Hilary Marquand, proposing the main toast, paid a tribute to the valuable work of the College in a wide variety of directions and to Dame Hilda Lloyd, its President. In particular, he referred to the importance of explaining the findings of science to the general public, which, as well as the medical profession, had an important part to play in overcoming the hazards of childbirth. In reply, Dame Hilda Lloyd described the continued progress of the College, which had been greatly honoured when Princess Elizabeth accepted the Fellowship earlier this year. The health of the guests was proposed by Mr. J. E. Stacey, and Sir Henry Cohen in a witty and apposite reply said that the Royal Colleges had an indispensable role in the future of the Health Service: in aiding the diffusion and extension of medical knowledge they stood for what was liberal and good, not for what was technological and utilitarian.

King's College Hospital Dinner

Under the chairmanship of Mr. A. C. Palmer the annual dinner for past and present students of King's College Hospital Medical School was held at Claridge's on September 29. It was a most successful occasion. About 150 King's men attended, though among them were regrettably few of the recently qualified or present students. The dinner has a central place in the celebrations marking the opening of the autumn session (see also p. 848), and this year to allow more opportunity for the renewal of old friendships speeches were cut to the barest minimum—an innovation which has everything to commend it at this type of function. Dr. J. L. Livingstone, in proposing the chairman's health, reviewed sympathetically and wittily Mr. Palmer's prowess on the rugger field, in the operating theatre, and on the golf course. Mr. Palmer proposed the health of the guests, mentioning particularly Dr. D. W. Logan, Dr. E. R. Boland, Mr. K. I. Julian, Dr. H. L. Glyn Hughes, and Mr. S. W. Barnes, house-governor of the hospital. Finally he paid a warm tribute to Sir Charlton Briscoe—"one of the greatest of King's physicians"—to which the latter replied.

Grey Turner Surgical Club

The club was founded last year for the purpose of surgical discussion and travel, and the late Professor Grey Turner gave his name to it and became president. At present there are seven members, and it is proposed to limit the number to ten. The first meeting was held in Birmingham in January, when members visited the Queen Elizabeth Hospital, watched several operations, and held discussions. One meeting a year is planned, and these will take place in different towns. The secretary is Mr. G. N. Bailey, 2, Lancaster Road, Harrogate.

B.M.A. Mission to Central and South America

At the end of September the four members of the B.M.A. good-will mission left for Rio de Janeiro to begin their visits to a number of universities in Central and South America. They are Dr. Francis Bach, Mr. A. L. Parry Brown, Dr. T. M. Ling, and Mr. T. Holmes Sellors. The visits are being arranged in co-operation with the Pan-American Medical Association, and the members of the team will give lectures and demonstrations on their special interests.

Blindness in the Colonies

Medical research will play the most important part in the campaign against blindness and eye diseases in the Colonies which was launched by the British Empire Society for the Blind last Empire Day. Six different ophthalmological and entomological surveys in the Colonies are planned, and it is hoped that the first of these combined teams will leave this country early in 1952 for West Africa. Entomologists are to work with the ophthalmologists on diseases known or suspected to be insect-borne. Effective control of the many pests that carry eye diseases will be a vital factor in reducing the incidence, since 80% of eye diseases in the Colonies are believed to be preventable. The society's surveys will be the first full-scale ophthalmological research work ever undertaken in the Colonies—at present reliable information is lacking because only partial surveys have been made. The society's campaign is meeting with a whole-hearted response in the Colonies themselves, where local Governments and influential citizens have rapidly grasped the potentialities of the campaign. Already 26 Colonies have formed local societies for the prevention of blindness and the welfare of the blind, the first buildings for the blind have actually been started, and teachers and organizers trained in this country are at work. Inquiries about the work of the society may be addressed to the Secretary, British Empire Society for the Blind, 53, Victoria Street, London, S.W.1.

Home for Child T.B. Contacts

Cardiff City Council has taken a large house which is to be used as a hostel for infants and very young children receiving B.C.G. vaccination after having been in contact with tuberculous households. Accommodation for about 20 children will be provided for a minimum of three months each. The home was opened on September 28 by the Lord Mayor of Cardiff.

The "Practitioner"

A thousand guests attended a reception at Claridge's Hotel on October 1 to celebrate the thousandth number of the *Practitioner*, the editor of which is Sir Heneage Ogilvie, and the assistant editor Dr. W. A. R. Thomson; Dr. Robert M. Stecher is associate editor in the U.S.A. Reference to the current special number of this journal is made in an annotation on another page.

Emergency Bed Service: Applications and Admissions

During the seven days ending October 1 the number of applications made by doctors to the London Emergency Bed Service for admission of patients was 779, of which 91.01% were admitted.

COMING EVENTS

St. George's Hospital Medical School

A series of lecture-demonstrations in neurology and psychiatry began at St. George's Hospital Medical School, Hyde Park Corner, London, S.W., on October 4 and will be continued on Thursdays at 4.30 p.m. until December 6. Admission is free to all medical practitioners and senior medical students.

Royal Institute of Philosophy

Sir Henry Cohen will give the Manson Lecture on "The Status of Brain in the Concept of Mind" at the Institute, 14, Gordon Square, W.C.1, on October 12 at 5.15 p.m.

Conference of Professional Nurses and Midwives

The thirty-sixth annual conference will be held at Seymour Hall, October 15 to 19, under the presidency of the Viscount Addison and convened by Sir Cecil Wakeley. It will open with the Blackham Memorial Lecture, which will be given by Sir William Gilliatt in honour of the late Major-General Blackham's service to the medical and nursing professions. Thereafter the conference will form a postgraduate course for nurses on modern trends in surgery, medicine, obstetrics and gynaecology, and therapeutics.

St. Thomas's Hospital Dinner

The St. Thomas's Hospital Old Students' Dinner will be held at the Trocadero Restaurant, Piccadilly Circus, London, W., on Friday, October 19, at 7 for 7.30 p.m., when the chair will be taken by Mr. A. C. Hudson. The price of the dinner, exclusive of drinks, is 29s. Dress, dinner jackets. Tickets may be obtained from the honorary secretaries, Old Students' Dinner, St. Thomas's Hospital, London, S.E.1.

Litchfield Lecture

This will be given by Professor Loyal Davis on October 10 at 5 p.m., at the Radcliffe Infirmary, Oxford. His subject will be "Physiological Principles Underlying the Treatment of High Diastolic Hypertension by the Thiocyanates and Sympathectomy."

U.C.H. Medical School Dinner

The annual dinner of past and present students will be held at the Savoy Hotel, W.C.2, on October 26, at 7.30 for 8 p.m. Tickets, price £1 7s. 6d., may be obtained from the Dinner Secretary, University College Hospital Medical School, University Street, W.C.1 (cheques made payable to U.C.H. Dinner Fund), and early application is advised. The customary series of postgraduate demonstrations will be held on October 25 and 26, from 10.30 a.m. to 4.45 p.m.

Leicester Royal Infirmary Old Residents' Dinner

Particulars of the dinner, which will be held on October 26, may be obtained from the joint secretaries, 384, London Road, Leicester.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday

Institute of Psychiatry, Maudsley Hospital, Denmark Hill, London, S.E.—October 8, 4.30 p.m., lecture-demonstration for postgraduates by Dr. E. Stengel.

Institute of Urology.—At St. Paul's Hospital, Endell Street, London, W.C., October 8, 10 a.m., *"Infections of the Urinary Tract other than Tubercle,"* by Mr. A. Clifford Morson; 11 a.m., *"Aetiology of Syphilis,"* by Dr. W. N. Mascall; 11.15 a.m., *"Laboratory Diagnosis of Infections,"* by Dr. R. Thomson; 2 p.m., *"Investigations of the Genito-urinary Tract,"* by Mr. A. R. C. Higham; 3.15 p.m., ward round, by Mr. J. D. Fergusson; 5 p.m., *"Sulphonamides and Antibiotics in Genito-urinary Infections,"* by Dr. A. H. Harkness.

Medical Society of London, 11, Chandos Street, Cavendish Square, W.—October 8, 8.30 p.m., annual general meeting; *"In Search of Truth,"* presidential address by Mr. A. C. Palmer.

●Middlesex Hospital Medical School (Clinical Lecture Theatre), Mortimer Street, London, W.—October 8, 4.30 p.m., *"The Genesis of Mammary Cancer in Mice,"* by Professor J. J. Bittner (University of Minnesota).

●Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.—October 8, 5 p.m., *"Islet Cell Tumours,"* by Professor Ian Aird; 6.15 p.m., *"Renal Calculus,"* by Mr. R. H. O. B. Robinson.

Tuesday

Chadwick Trust.—At Royal Society of Tropical Medicine and Hygiene, 26, Portland Place, London, W., October 9, 2.30 p.m., *"Some International Aspects of Environmental Hygiene,"* by Mr. F. E. Bruce, M.Sc.

Chelsea Clinical Society.—At South Kensington Hotel, 41, Queen's Gate Terrace, London, S.W., October 9, 7 for 7.30 p.m., *"Some Medical Problems in High Speed and Altitude Flying,"* by Group Captain W. K. Stewart; *"Medical Problems of Civil Aviation,"* by Dr. J. E. Gabb. Discussion.

Edinburgh University.—At Anatomy Lecture Theatre, University New Buildings, Teviot Place, Edinburgh, October 9, 5 p.m., *"Hormones of the Adrenal Cortex in Clinical Medicine,"* by Professor E. C. Kendall (Minnesota).

●Institute of Dermatology, Lisle Street, Leicester Square, London, W.C.—October 9, 5.30 p.m., *"Connective Tissue,"* by Dr. E. J. Moynahan.

Institute of Urology.—At St. Paul's Hospital, Endell Street, London, W.C., October 9, 10 a.m. and 11.15 a.m., *"Genito-urinary Tuberculosis,"* by Mr. F. J. F. Barrington; 11 a.m., *"Pathology and Immunology of Syphilis,"* by Dr. C. E. Dukes (see also October 10); 3.15 p.m., *"A Survey of the Methods of Prostatectomy,"* by Mr. R. Ogier Ward; 5 p.m., *"Stress Incontinence,"* by Mr. H. Rees. At St. Peter's Hospital, Henrietta Street, London, W.C., October 9, 2 p.m., *"Retropubic Prostatectomy,"* demonstration by Mr. A. W. Badenoch.

Leeds University.—At University Union (Riley-Smith Hall), Leeds, October 9, 3 p.m., *"The Sick Man and the Community,"* inaugural lecture of the Faculty of Medicine by Dr. J. R. Rees. Members of medical profession welcome.

●Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.—October 9, 5 p.m., *"The Clinical Use of Radio-active Di-Iodo-Fluorescein in the Diagnosis and Surgical Treatment of Tumours of the Central Nervous System,"* Moynihan Lecture by Professor Loyal Davis (Northwestern University, Chicago); 6.15 p.m., *"Coarctation of the Aorta,"* by Mr. C. Price Thomas.

Wednesday

Glasgow University: Department of Ophthalmology.—October 10, 8 p.m., *"The Eye in Hypertension (II),"* by Dr. R. Leishman.

●Institute of Dermatology, Lisle Street, Leicester Square, London, W.C.—October 10, 5.30 p.m., *"X-ray Technique,"* by Dr. C. W. McKenny.

Institute of Urology.—At St. Paul's Hospital, Endell Street, London, W.C., October 10, 10 a.m., *"Aetiology, Pathology, Symptoms, and Indications for Treatment in Prostatic Enlargement,"* by Mr. H. K. Vernon; 11 a.m., *"Pathology and Immunology of Syphilis,"* by Dr. C. E. Dukes (see also October 9); 11.15 a.m., *"Endoscopic Operations on the Prostate,"* by Mr. R. Ogier Ward; 2 p.m., museum demonstration, by Mr. D. I. Williams; 3.15 p.m. and 5 p.m., *"Calculous Disease,"* by Mr. H. P. Winsbury-White; 4.30 p.m., *"Prostatic Cancer,"* by Mr. J. D. Fergusson.

Oxford University.—At Radcliffe Infirmary, Oxford, October 10, 5 p.m., *"Physiological Principles Underlying the Treatment of High Diastolic Hypertension by the Thiocyanates and Sympathectomy,"* Litchfield Lecture by Professor Loyal Davis.

Royal Army Medical College.—At Lecture Theatre, John Islip Street, London, S.W., October 10, 5 p.m., *"A Gastric Gossip,"* by Sir Arthur Porritt.

●Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.—October 10, 5 p.m., *"Surgical Treatment of Cirrhosis of the Liver,"* Hunterian Lecture by Professor F. E. Stock; 6.15 p.m., *"Renal Pain,"* by Mr. J. B. Oldham.

Royal Statistical Society: Study Section.—At Electric Lamp Manufacturers' Association of Great Britain, 2, Savoy Hill, London, W.C., October 10, 6 p.m., *"Some Statistics of a London Undergraduate Teaching Hospital Covering the Last Sixty Years,"* by Mr. F. D. Bushell.

Society of Chemical Industry: Microbiology Group.—At Institution of Structural Engineers, 11, Upper Belgrave Street, London, S.W., October 10, 2.15 p.m., *"The Use of Isotopes in Microbiology."* Symposium.

Thursday

Alfred Adler Medical Society.—At 11, Chandos Street, London, W., October 11, 8 p.m., *"Kretschmer's Approach to Constitutional Psychiatry,"* by Dr. E. B. Strauss. Discussion to be opened by Drs. Emanuel Miller and E. K. Ledermann.

Honyman Gillespie Lecture.—At University New Buildings (Anatomy Theatre), Teviot Place, Edinburgh, October 11, 5 p.m., *"Tuberculosis: An Incident or a Disease?"* by Professor Charles Cameron.

●Institute of Dermatology, Lisle Street, Leicester Square, London, W.C.—October 11, 5.30 p.m., *"Histopathology—Diseases Involving the Collagen,"* by Dr. H. Haber.

Institute of Orthopaedics, Royal National Orthopaedic Hospital, 234, Great Portland Street, London, W.—October 11, 8.30 p.m., "*A Study of 762 Patients with Spinal Cord Injuries*," by Professor Loyal Davis (Northwestern University, Chicago).

Institute of Urology.—At St Paul's Hospital, Endell Street, London, W.C., October 11, 10 a.m., "*Anuria*," by Mr. F. R. Kilpatrick; 11 a.m., "*Primary Syphilis*," by Dr. W. N. Mascall; 11.15 a.m., "*Tumours of Kidneys and Ureter*," by Mr. H. Rees; 2 p.m., "*Injuries of Kidney and Ureter*," by Mr. A. W. Badenoch; 3.15 p.m., "*Congenital Anomalies of Kidney and Ureter*," by Mr. J. G. Sandrey.

●Royal College of Obstetricians and Gynaecologists, 58, Queen Anne Street, London, W.—October 11, 5 p.m., "*The Causes and Management of Premature Birth*," John Shields Fairbairn Memorial Lecture by Dr. Nicholson J. Eastman (Johns Hopkins Hospital, Baltimore, U.S.A.).

●Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.—October 11, 5 p.m., "*Thyrotoxicosis*," Cecil Joll Lecture by Sir Thomas Dunhill; 6.15 p.m., "*Practical Considerations in the Surgery of the Hand and Fingers*," by Mr. Eric Farquharson.

St. George's Hospital Medical School, Hyde Park Corner, London, S.W.—October 11, 4.30 p.m., lecture-demonstration in psychiatry by Dr. D. Curran.

Friday

Edinburgh Postgraduate Board for Medicine.—At Anatomy Lecture Theatre, University New Buildings, Edinburgh, October 12, 5 p.m., "*Aureomycin*," by Dr. Benjamin Duggar (University of Wisconsin).

●Institute of Dermatology, Lisle Street, Leicester Square, London, W.C.—October 12, 5.30 p.m., "*Scleroderma, Granuloma Annulare*," clinical demonstration by Dr. G. B. Dowling.

Institute of Urology.—At St. Paul's Hospital, Endell Street, London, W.C., October 12, 10 a.m., "*Marion's Disease and Diverticula of the Bladder*," by Mr. R. Ogier Ward; 11 a.m., "*Secondary Syphilis*," by Mr. A. H. Harkness; 2 p.m., "*Treatment of Tuberculosis*," by Mr. F. R. Kilpatrick; 3.15 p.m., Demonstration of *X* Rays, by Mr. J. E. Semple; 5 p.m., "*Gonococcal Urethritis*," by Dr. W. N. Mascall. At St. Peter's Hospital, Henrietta Street, London, W.C., October 12, 11.15 a.m., museum demonstration by Mr. H. K. Vernon.

Kent and Canterbury Hospital, Canterbury.—October 12, 8 p.m., clinical meeting.

London Association of the Medical Women's Federation.—At Royal Free Hospital School of Medicine, 8, Hunter Street, London, W.C., October 12, 8.30 p.m., annual general meeting.

London University.—At University College Hospital Medical School, University Street, Gower Street, London, W.C., October 12, 5 p.m., "*Premature Rupture of the Membranes: Its Bearing on Maternal Febrility and Infant Outcome*," first of two special university lectures in medicine by Professor N. J. Eastman (Johns Hopkins University). (*See also October 15.*)

●Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.—October 12, 5 p.m., "*Surgical Relief of Pain*," by Professor Lambert Rogers; 6.15 p.m., "*Cancer of the Skin*," by Sir Stanford Cade.

Royal Institute of Philosophy, 14, Gordon Square, London, W.C.—October 12, 5.15 p.m., "*The Status of Brain in the Concept of Mind*," Manson Lecture by Sir Henry Cohen.

Royal Medical Society, 7, Melbourne Place, Edinburgh.—October 12, 8 p.m., "*Spinal Man*," by Mr. I. G. Lennox.

Saturday

Institute of Urology.—At St. Paul's Hospital, Endell Street, London, W.C., October 13, 10 a.m., "*Cystic Disease of the Kidney*," by Mr. J. D. Fergusson; 11.15 a.m., "*Neoplasms of the Urethra, Penis, and Scrotum*," by Mr. D. I. Williams.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Cox.—On September 27, 1951, at Nuffield House, Guy's Hospital, London, S.E., to Betty (formerly Padbury), wife of Dr. A. G. Charlton Cox, a son—James George.

Morgan.—On August 22, 1951, at Galt Hospital, Lethbridge, Alberta, Canada, to Helen (formerly James), wife of John E. Morgan, M.R.C.O.G., a son—David John.

Murley.—On September 29, 1951, to Elizabeth Mary (formerly Price), wife of Dr. David R. Murley, of Polmenna, Falmouth, Cornwall, a daughter.

Swan.—On September 21, 1951, at Lady Margaret Nursing Home, London, W., to Diana (formerly Sturges), wife of Dr. John H. Swan, a daughter.

MARRIAGES

Caira—Senior.—On September 25, 1951, at St. Andrew's Cathedral, Glasgow, Dr. Eugene G. Caira, of 45, Albert Road, Gaurock, Renfrewshire, to Anne Senior, of Langcliffe Cottages, Kettlewell, Yorks.

DEATHS

Card.—On September 23, 1951, at 47, Cassiobury Park Avenue, Watford, Herts, Alfred Herbert Card, M.R.C.S., L.R.C.P., late of Muswell Hill, London, N.

Davy.—On September 25, 1951, at Melbourne, Philip Claude Tresilian Davy, C.M.G., M.B., Lieutenant-Colonel, R.A.M.C., retired, aged 74.

Dow.—On September 22, 1951, at Oirig Bank Nursing Home, Kendal, James Fleming Dow, M.D., of Uplands, Arnside, Westmorland.

Hudleston.—On September 22, 1951, at Eastbourne, Ivor Robert Hudleston, D.S.O., M.R.C.S., L.R.C.P., Lieutenant-Colonel, R.A.M.C., retired.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

A Typical Lag Curve

Q.—*What is the prognosis for a man of 35 in whom glycosuria has been discovered to be due to "a typical lag curve"? He has been rejected for military service because of this finding.*

A.—The prognosis is very good, but it must be remembered that the patient is as likely, but probably no more likely, than anyone else to develop diabetes. If this does occur, there is usually some delay in making the diagnosis, which can be made only by a sugar tolerance test. A family history of diabetes may be misleading, as the other members may also have had an innocent glycosuria, but if genuine should ensure periodical investigations. The sugar tolerance curve should always be repeated before any operation is performed.

Linoleic and Linolenic Acids

Q.—*What are the therapeutic actions of linoleic acid and linolenic acid when given by mouth or inunction? A patient who had been taking a capsule containing 0.4 g. of the ethyl esters of these acids once daily for 10 days had an attack of tetany. Is this likely to have been related to the therapy?*

A.—In 1929 evidence was published by G. O. Burr and M. M. Burr that, when rats are given a diet containing no fat, in course of time they develop skin lesions due to desquamation, and also necrosis of the tail. Investigation showed that these changes were due to the absence of unsaturated fatty acids, and that the most effective ones in preventing the changes were linoleic and linolenic acids. In 1933 Hansen attempted a clinical application of these findings by treating children who were suffering from chronic eczema with fats rich in these two acids. Good results were obtained. Since that time linoleic and linolenic acids have been used with success in some cases of eczematous furunculosis (in adults), in psoriasis, in infantile eczema, in chronic leg ulcers, and in chronic furunculosis. Treatment may have to be continued for three months. It is quite possible that the administration of ethyl esters of these acids might produce tetany. After the esters are split, the free fatty acids may combine with calcium and prevent the absorption of that element in sufficient quantities.

Medical Treatment of Gallstones

Q.—*Is there any medical treatment of gallstones which can cause them to dissolve or be passed into the gut? I have heard of practitioners who have given liquid medicine which caused severe pain but resulted in the passage of a number of fairly large gallstones.*

A.—There is no medical treatment of gallstones which will lead them to dissolve or be passed into the gut. Olive oil has been used extensively, and produces some relief in gall-bladder disease largely by reducing the symptom of flatulence. It quite often results in the passage of faecal concretions *per rectum* that closely resemble calculi and have been regarded by patients as gallstones. Pethidine in acute biliary colic relieves pain and does not cause spasm of the sphincter. Thus small stones may be passed after it has been given, but it has no direct action in expelling them.

New Treatments of Peptic Ulcer

Q.—*In the treatment of peptic ulcers is (1) "robaden" or (2) cabbage juice of any value? What are the details of cabbage-juice therapy, if it is useful?*

A.—(1) Robaden preparations (variously spelt as robadin and robuden) are, to quote the manufacturers, "protein-free extracts obtained from the tissue of the stomach and small intestine of freshly slaughtered young animals." For the treatment of gastric ulcers a preparation is recommended which is obtained predominantly from the stomach, and for the treatment of duodenal ulcers one is obtained predominantly from the small intestines. Experimentally, robaden has been found to be effective in the prevention of ulcers in guinea-pigs (Roulet, F., *Schweiz. med. Wschr.*, 1945, 75, 912) and in rats (Grandjean, E., *Rev. méd. Suisse rom.*, 1948, 68, 442). A large number of clinical reports have been published on the Continent; a list of references is given by J. B. Stolte (*Lancet*, 1950, 2, 858). The only reports available in the British press are those of O. Hubacher (*Lancet*, 1946, 2, 272) and Stolte. The reports have mostly been favourable, but with the exception of Stolte's they have consisted in accounts of the progress of groups of cases, uncontrolled by comparison with other treatments. Stolte carried out a "blind trial" in which he did not know, at the time of treatment, which of his patients were receiving robaden and which were receiving a placebo; he obtained equally good results with both drugs.

Similar extracts were prepared at an earlier date in America, and much experimental work has been done by Ivy and his colleagues with the preparation which they call enterogastrone. There is no doubt of the physiological activity of enterogastrone, nor is there of the urinary extract (urogastrone) obtained by Sandweiss. Clinical trials in America have, however, been disappointing. It is not possible to be dogmatic at this stage about the use of robaden, but the weight of evidence would appear to be against it. Further controlled trials are desirable.

(2) The use of cabbage juice in the treatment of peptic ulcer is based upon the work of Cheney, who found that it was possible to prevent histamine-induced ulcers in guinea-pigs by the addition of a number of foods to their diet, the most effective of which was fresh cabbage. Boiled cabbage was ineffective, and so were all the known vitamins. Cheney has reported satisfactory results in the great majority of 65 cases treated with one quart of freshly prepared cabbage juice daily, and has claimed extremely rapid healing of ulcer craters (Cheney, G., *J. Amer. diet. Ass.*, 1950, 26, 668). The treatment awaits fuller trial.

Cigarette-lighters and Cancer

Q.—*In the research into the incidence of lung carcinoma, has any attempt been made to correlate its incidence among smokers with the increasingly fashionable use of the cigarette-lighter, whose vapours must surely contain carcinogenic substances?*

A.—No consideration has been given to the possibility that the vapours from cigarette-lighters may be of importance in the aetiology of lung carcinoma in any published work. The possibility is being investigated in work now in progress, and results should be available in about a year's time.

Fitting of a Dental Bridge

Q.—*A girl of 15 has a gap due to the removal of her left upper central incisor, and now wears a plate. What is the earliest age at which a bridge can be fitted, and will it keep the teeth in position?*

A.—A bridge can be fitted in the next few years, preferably about the age of 17 or 18. The supporting teeth will, of course, be kept in their relative positions when the bridge is in place. In the case of a missing central incisor the supporting teeth must be strong and fairly large attachments made, for although the lateral incisors do not usually get a great deal of leverage upon them the central incisors are far more subject to stresses and strains.

Rapid Dental Decay

Q.—*What are the causes of very rapid dental decay, and what treatment is advocated? In a woman of 30 dislodgment of a stopping is followed by complete disappearance of the crown down to the gum margin in a month or two. Her front teeth are still intact. What can be done to preserve them?*

A.—There are many associated causes of rapid dental decay, but the precise aetiology of the condition is still obscure. Rapid decay may be related to faulty diet, stagnation of food, and lack of oral hygiene, and may be accelerated by faulty structure of the teeth. In a woman of 30, as the teeth will all be fully formed and normally fully erupted, their structure cannot be improved. Attention should be given therefore to the diet; so far as possible meals should end with some form of fibrous food to cleanse the teeth mechanically. Also regular and frequent visits to the dental surgeon should be made so that any caries may be properly extirpated and fillings inserted.

Mountain Sickness

Q.—*What are the causes of mountain sickness? How may it be prevented and treated?*

A.—Mountain sickness is a very large subject which cannot adequately be dealt with in a short space. Its signs and symptoms are not necessarily equivalent to those experienced by aviators, and the following remarks apply only to the untoward effects of altitude experienced on mountains. An acute form occurs in susceptible individuals if they are suddenly raised, for instance by train, to quite moderate heights, symptoms having been recorded at as low as 7,000 ft. (2,134 m.). The main symptoms are nausea and vomiting. A more chronic form is experienced by unacclimatized people at great altitudes even when these altitudes have been reached slowly. Symptoms may occur at as low as 13,000 ft. (3,962 m.). The most important symptom is lassitude. Mountaineers have also reported lack of concentration, breathlessness on the slightest exertion, sleeplessness, irritability, mental confusion, headache, and loss of appetite.

Mountain sickness can be to a large extent prevented by slow acclimatization. Mountaineers in good training seldom experience any symptoms below 18,000 ft. (5,486 m.). Above this, if they are to avoid the consequences of oxygen lack, upward progress must be slow, an average of only 1,000 ft. (305 m.) a day being the limit for most people. Even with this precaution breathlessness on exertion may be severe, although the other symptoms are avoided. Acclimatization appears to reach its limit of usefulness at about 24,000 ft. (7,305 m.). At higher altitudes the symptoms return and a general physical deterioration with loss of weight sets in within a few days.

The only treatment is the administration of oxygen or a return to normal levels.

Correction.—In our Medico-Legal report on "Mental Defectives' Attack" (September 22, p. 741) we incorrectly described Darenth Park Hospital as a mental hospital, but it is in fact a mental deficiency institution.

All communications with regard to editorial business should be addressed to The Editor, British Medical Journal, B.M.A. House, Tavistock Square, London, W.C.1. Telephone: Euston 4499. Telegrams: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.
Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs.
ADVERTISEMENTS should be addressed to the Advertisement Manager, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.). Telephone: Euston 4499. Telegrams: *Britmedads, Westcent, London.*
MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association Telephone: Euston 4499. Telegrams: *Medisecra, Westcent, London.*
B.M.A. Scottish Office: 7, Drumsheugh Gardens, Edinburgh.